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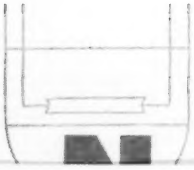

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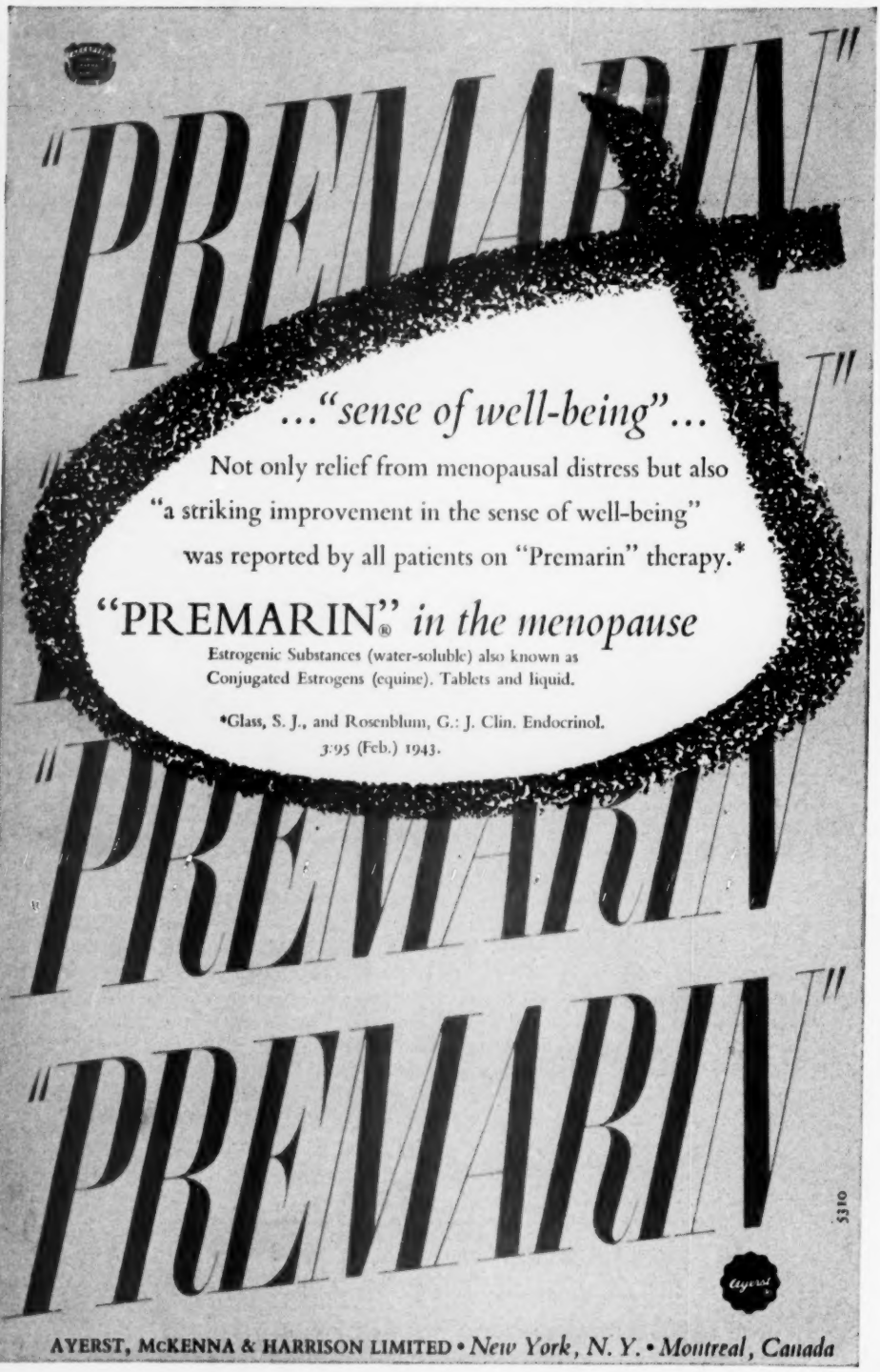
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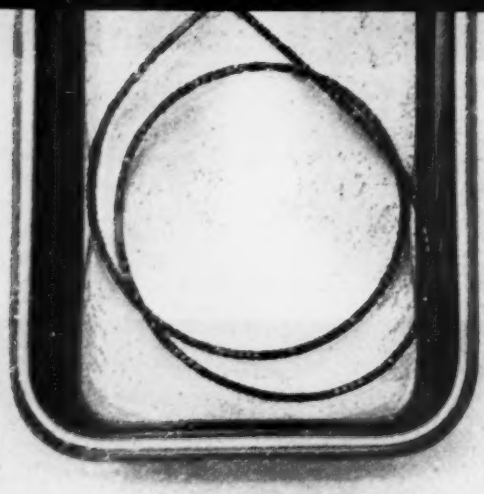

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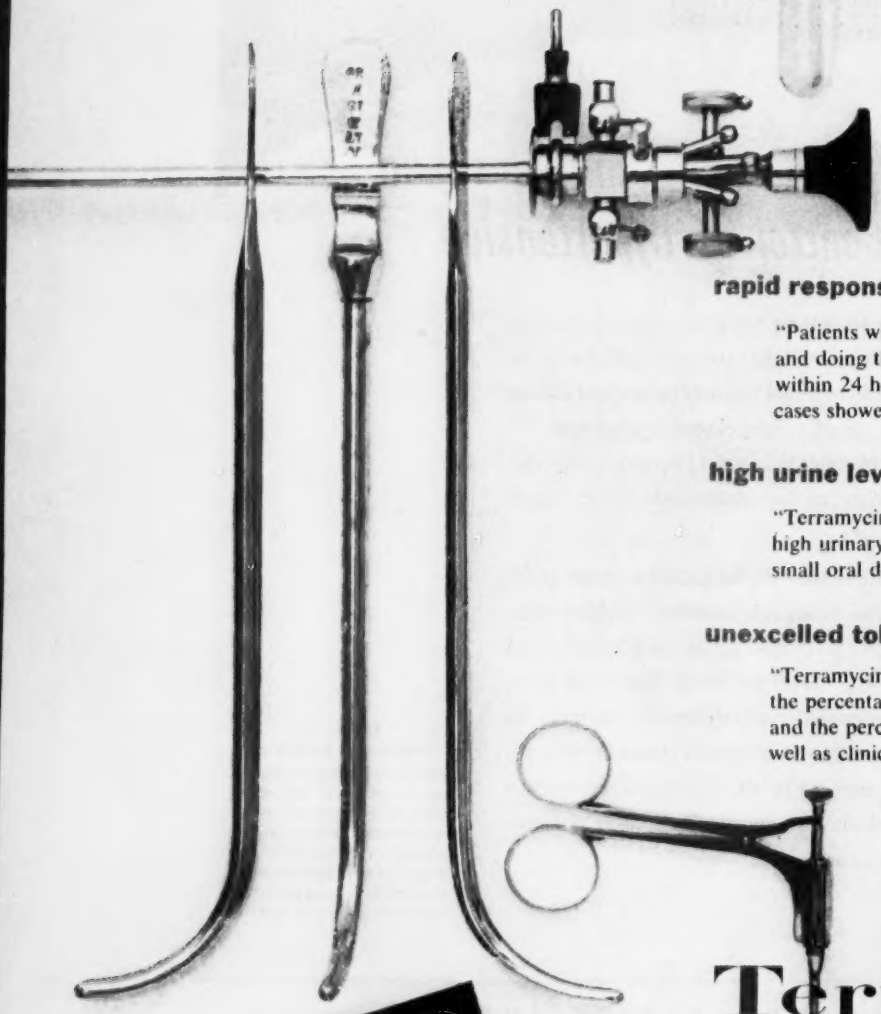

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1. Canad. M. A. J. 66:151 (Feb.) 1952.
2. J. Urol. 67:762 (May) 1952.
3. Ibid. 69:315 (Feb.) 1953.

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1. Howard, J. E. Protein Metabolism During Convalescence After Trauma. Arch. Surg. 50:166, 1945.
2. Co Tui, Minutes of the Conference on Metabolism Aspects of Convalescence Including Bone and Wound Healing. Josiah Macy, Jr. Foundation, Fifth Meeting Oct. 8-9, p. 57, 1943.
3. Whipple, G. H. and Madden, S. C. Hemoglobin, Plasma Protein and Cell Protein: Their Interchange and Construction in Emergencies. Medicine 23:215, 1944.
4. Mulholland, J. H., Co Tui, Wright, A. M., Vinci, V., and Shafiroff, B. Protein Metabolism and Bed Sores. Am. Surg. 118:1015, 1943.

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Volume 248 JUNE 11, 1953 Number 24

OBSERVATION AND EXPERIMENT*

A. Bradford Hill, C.B.E., D.Sc., Ph.D.†

LONDON, ENGLAND

TWO years ago, in his Cutter Lecture, one of my predecessors pointed out that the object of any science is "the accumulation of systematized verifiable knowledge," and that this is to be achieved through "observation, experiment and thought" — the last including both criticism and imagination. He then added, "the use of the experimental method has brilliant discoveries to its credit, whereas the method of observation has achieved little."[1] This dictum must surely prove, at least at first sight, more than a little disconcerting to the exponent of preventive medicine. In dealing with the characteristics of human populations, in sorting out the features of the environment that are detrimental from those that are beneficial, he does not often find it easy to experiment. The method of observation frequently plays a large part in the particular study of mankind that is his prerogative. Is it, then, quite so useless? Must he give it up as merely a time-wasting hobby?

Looking farther back in time I found that these questions had been considered, as indeed I had expected, by my statistical forebears and teachers in Great Britain. They did not perhaps have quite so pessimistic an outlook as the one I have quoted above, but they certainly did not underrate the difficulties of the observational approach or overlook the value of the experimental method. Thus, in 1924, Yule's[2] view was that the student of social facts could not experiment but had to deal with circumstances operating entirely beyond his control; he must accept records simply of what has happened. He wrote:

> The expert in public health, for example, must take the records of deaths as they occur, and endeavour as best he can to interpret, say, the varying incidence of death on different districts. Clearly this is a very difficult matter...The purpose of *experiment* is to replace these highly complex tangles of causation, [and] the more perfect the experiment — the more nearly the experimental ideal is attained — the less is the influence of disturbing causes, and the less necessary the use of statistical methods.

Greenwood[3] has a characteristic passage, which I quote in full since I believe that the part of it that has no close bearing on my present thesis will nevertheless more than bear repetition today;

> My conception of the statistical method in medicine has changed in the last 20 years; this is especially so with regard to the bearing of statistical method upon experiment. I used to see in the statistician the critic of the laboratory worker: it is a rôle which is gratifying to youthful vanity, for it is so easy to cheat oneself into the belief that the critic has some intellectual superiority over the criticised. I do not think even now that statistical criticism of laboratory investigations is useless, but I attach enormously more value to direct collaboration, the making of statistical experiments, and the permeation of statistical research with the experimental spirit.

The last words — written nearly thirty years ago — are, I suggest, the operative clause in the present setting — the permeation of statistical research with the experimental spirit. Although, as Yule said, facts must often, inevitably, be accepted as they occur, one does not have merely to accept facts as they are reported. One need not accept as final what some third party can give, or chooses to give — for example, a registrar-general or a census bureau. Such reported observations may, of course, prove to be a most valuable indicator of a problem; they may be, thereby, the starting point of research. But when the pattern of cause and effect is complicated they are often not likely to provide a solution. The methods of partial correlation, enthusiastically accepted a quarter of a century ago, no longer seem to have an "unlimited power to penetrate the secrets of nature."[4] One must go seek more facts, paying less attention to technics of handling the data and far more to the development and perfection of methods of obtaining them. In so doing one must have the experimental approach firmly in mind. In other words, can observations be made in such a way as to fulfil, as far as possible, experimental requirements?

Ancient Observation (the Cholera)

It was in this way, nearly a hundred years ago, that John Snow approached his problem, not only as an incomparable master of logical deduction from observations but also, it should be noted, as the

*The Cutter Lecture on Preventive Medicine, delivered at the Harvard School of Public Health, March 25, 1953.

†Professor of medical statistics and director of the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine; honorary director, Statistical Research Unit of the Medical Research Council, England.

constructor of observations. To recapitulate briefly, his opening arguments are based on vital statistics of the different areas of London. Using the deaths given in the first report of the Metropolitan Sanitary Commission (1847), he first shows the excessive mortality from cholera that in the epidemic of 1832 befell the districts supplied by the Southwark Water Works, a company that drew its water from the Thames at London Bridge and provided worse water, according to Snow, than any other in the metropolis. Even the order of precedence between a flea and a louse is sometimes, it appears, of importance. A death rate from cholera of 11 per 1000 inhabitants stands out starkly amidst the rates of 2, 3 and 4 for other districts of the city, but clearly that unenviable record might be explicable in terms of some quite different local characteristic. The evidence gives a lead but no more. The case is somewhat, but not at all convincingly, strengthened by the events of 1849. The highest mortality rates from cholera were again consistently to be found in the districts supplied by the Southwark Company (now combined with the South London Water Company to form the Southwark and Vauxhall) and also in those served by the Lambeth Company; both companies drew their water from the Thames in its most contaminated reaches. In 1853 there begins to appear reason to sit up and even to take notice. The Lambeth Company had removed its works from central London to Thames Ditton, where the river was wholly free from the sewage of the metropolis; the Southwark and Vauxhall Company continued to prescribe for its customers the mixture as before. In the 12 subdistricts served by the latter 192 persons died of cholera in the epidemic of 1853 — with 168,000 persons living the crude rate is thus 114 per 100,000. In 16 subdistricts served by both companies 182 perons died; among 301,000 living, that is a rate of 60 per 100,000. In three subdistricts of 15,000 persons served only by the Lambeth Company no deaths from cholera were reported.

So far do the statistical observations run; so far but not far enough. On that showing alone one might even hesitate to accept Snow's "very strong evidence" against the water supply. He himself was indeed of that mind, for "the question," he observed, "does not end here" (he had no intention of letting it end there). It was not said without reason that wherever cholera was visitant there was he in the midst. He noted that the Southwark and Vauxhall and Lambeth companies were competitors so that in some subdistricts the pipes of each went down all the streets and into nearly all the courts and alleys:

> Each Company supplies both rich and poor, both large houses and small...No fewer than 300,000 people of both sexes, of every age and occupation, and of every rank and station, from gentlefolk down to the very poor, were divided into two groups without their choice, and, in most cases, without their knowledge; one group being supplied with water containing the sewage of London, and, amongst it, whatever might have come from the cholera patients, the other group having water quite free from such impurity.

Here, then, was an unwitting experiment on the grandest scale, and Snow set himself to learn its results.

In 1854, with one medical man to assist him, up and down the streets, courts and alleys of South London he tramped in the summer's sun, learning for every cholera death the water supply of the household. Thus, by personal, persistent and accurate field work were the basic vital statistics infinitely strengthened. In 40,000 houses served by the Southwark and Vauxhall Company 286 fatal attacks were found in the first four weeks of the epidemic of 1854 — 71 deaths per 10,000 households; in 26,000 houses served by the Lambeth Company 14 fatal attacks were found — only 5 deaths per 10,000 households. In such a way was observation successfully added to observation to form a coherent and convincing whole.

It might be argued that Snow was lucky in having at hand a natural "experiment." Perhaps he was. But such "experiments" or, at the least, effective "controls" would not, I believe, really prove to be so rare if one invariably cast one's eyes round for them after vital statistics, or similar observations, had given an appropriate lead.

Certainly, in the famous Broad Street Pump outbreak of cholera no experiment offered. Its story is too well known to need any detailed reference here, but having brought Snow into my picture, I could not bear to pass it by wholly unsung. It is not so much for persuading the local board of guardians to remove the handle of the pump that Snow here deserves credit — though for this alone it is often paid to him. In fact either through the flight of the terrified population from the stricken area (and Snow himself says that "in less than 6 days the most afflicted streets were deserted by more than three-quarters of their inhabitants") or through natural epidemiologic causes, the outbreak had been steeply declining for five or six days before the well was thus put out of action. That "experiment" provides no useful evidence.

It is again in the field work that his strength lies: the map showing the concentration of deaths around the pump with their number diminishing greatly, or ceasing altogether, at each point where it became decidedly nearer to send to another pump; the demonstration of the escape of the inmates of the workhouse, which had its own well, and, similarly, of the 70 workmen in the brewery who knew better than to drink water — or if somehow driven to do so drew from a well within the brewery. And the striking individual histories, the most conclusive of which Sherlock Holmes might well have called "the curious case of the Hampstead widow." In the weekly return of births and deaths of September 9 published by the Registrar-General of England and

Wales there appeared the following entry: "At West End [Hampstead], on 2nd September, the widow of a percussion-cap maker, aged 59 years, diarrhoea two hours, cholera epidemica sixteen hours." (The times refer to the duration of the fatal illness, then — and again now — entered by the medical practitioner upon the certificate of cause of death.) One of the factories in Broad Street made percussion caps, but on inquiry Snow found that the widow had not been in the neighborhood for many months. However, she still preferred the water from the pump to that of the more salubrious neighborhood to which she had retired, and she commissioned a carter who drove daily between the two points to bring her a large bottle. The bottle was duly delivered on August 31. She drank of it and died two days later. A niece on a visit to her likewise drank of it. She then returned to her home in Islington, where she died of cholera. There was no cholera extant in either neighborhood.

To digress for a moment, there was at least one other person who drank of that bottle. The story here is, perhaps, less well known. The first medical officer of health for Hampstead (now one of the metropolitan boroughs of London) dictated as an old man in 1889 some recollections under the title of "The Sanitary Experiences of Charles F. J. Lord, M.R.C.S." It is now held in manuscript in the Hampstead Public Library but was privately printed for circulation among the old man's friends. There is a copy in the library of the Surgeon General in Washington under the title, "Jottings: Some experience with reflections derived through life and work in Hampstead from 1827 to 1877" (Pamphlet Vol. 3807). Lord himself died before making final corrections of the proofs. On pages 36 and 37 of the printed version the following passage is included:

> A memorable case of what we may consider an imported cause of disease happened at West End; Mrs. Eley Mother of the renowned firm "Eley Brothers" had lived in Broad Street Soho, and had drunk with glorification from a deep well there situated. On leaving London, she had a big stone bottle brought daily for the use of herself at West End. Summoned hastily to see the old lady I found her in the early stage of Cholera — remedies were unavailing, though solicitously applied in every way by a daughter and one of her sons. A consultation with the highly esteemed Dr. Farre ensued, the Patient never rallied, died that night. The cause of the disease at that time was never suspected; it was proved afterwards by the untiring investigations of Dr. Snow, that the water from the Broad Street well was contaminated and produced the disease; a sort of practical joke arose among the Teetotalers of the Broad Street district; those who stuck to the Porter especially those of the Brewery were rarely victims to the disease while those who drank the water fell fast around. I myself while attending closely on the old lady, as also was her daughter, was much troubled with Diarrhoea having unsuspiciously sipped some of the imported water. This insipient [*sic*] stage of Cholera soon passed away, in the absence of full or renewed doses.

Here, then, to return to my thesis, is a masterpiece — many persons would say *the* masterpiece — of observation and logical inference, made many years before the discovery of the vibrio of cholera. It shows — as many other examples have shown — that the highest returns can be reaped by imagination in combination with a logical and critical mind, a spice of ingenuity coupled with an eye for the simple and humdrum, and a width of vision in the pursuit of facts that is allied with an attention to detail that is almost nauseating.

Modern Observation (Rubella)

A modern example of acute observation lies in the story of rubella in pregnancy unfolded, almost a hundred years later, in Australia. Again, the story is too well known to need retelling, but it has a facet perhaps less familiar and yet of great interest to the student of public health — in other words, to the observer of group phenomena. It might well be that the congenital defects observed in Australia in the years 1938 to 1941 were something new in medicine, that the rubella epidemic was of a particular virulence, or that the virus had acquired some unusual characteristic at that time. Indeed, there is so much folklore attached to events in pregnancy that if the effects of German measles were an old phenomenon one might possibly have expected to find some old-wives' tale concerning it. I know of none in Britain. That the story was not, however, new in Australia is strongly indicated by the statistical observations marshaled by Lancaster.[5] In each of the reports on the Australian censuses of 1911, 1921 and 1933 there is a section that deals with the enumerated prevalence of blindness and deaf-mutism. The incidence of the latter is revealing; it shows a maximum in each census corresponding to persons born in the years 1896-1900.

At the census of 1911 the peak lay in the age group from ten to fourteen, and the statistician, writes Lancaster, "was inclined to ascribe the maximum to the more complete enumeration of the deaf at the school ages"; most observers would, I suspect, have taken that view. When, however, in 1921, the peak shifted to the age group twenty to twenty-four the statistician considered epidemic disease as a possible cause. He suggested that the increased incidence of deafness at certain ages might synchronize with the occurrence of such illnesses as "scarlet fever, diphtheria, measles, and whooping cough." In the report on the census of 1933 infective disease was again discussed. But the lead given by the somewhat crude vital statistics was not, it appears, followed up at the time. Lancaster himself has followed it up — in 1951 and therefore, of course, after the clinical observations of 1938-41 — by examining the dates of birth of children admitted to institutions for the deaf and dumb. He finds, to take a single example, that of those admitted in New South Wales 15 were born in 1898 and 16 in 1900. For the intermediate year 1899 the figure soared to 70. Furthermore, these 70 are not evenly spread throughout the year but are concentrated in the months

of April to September. On such evidence, marshaled in detail and with skill, Lancaster concludes that "deafness has appeared in epidemic form in Australia in the past, notably among children born in 1899, 1916, 1924, 1925 and in 1938-41" and that "there is some presumptive evidence that all these epidemics, with the exception of that in 1916, were caused by antecedent epidemics of rubella." It seems so easy *now*, he rightly observes, to suggest a causal relation; it is always easy to be wise after the event. Nevertheless, there was at least a legible scrawl on the wall — additional and accurate data were there for the seeking and, once sought, offered a clear case for a carefully designed field inquiry. The combined observational and statistical approach could have won the day; it could have won it quite a long time ago.

Cancer of the Lung

This approach seems to me to be the only one possible in another matter of community concern today — the etiology of carcinoma of the lung. The starting point is as usual the national registration system. "It is sometimes asked," says Stocks,[6] "how statistics can cure disease," and he suggests that one may counter the question by another question: "how many researches which have led to real advances in Medicine would ever have been started had there not first been some statistics to suggest that here was a problem to be investigated?" In this particular instance it is, of course, admitted that skill in, and modern adjuncts to, diagnosis make more than dubious the whole gamut of changes that the system of vital statistics reveals. But there is, in my opinion, more than enough evidence to regard some of that change as real and to justify a search for a cause of a truly rising mortality in England and Wales. Aided and abetted by the Medical Research Council, Doll and I set about that search in 1947. Our aim was to make the field observations mirror an experimental design as nearly as possible. For each patient with cancer of the lung we sought a "control" patient with some other disease — a patient of the same sex, of the same age group, in the same hospital at or about the same time, but otherwise chosen at random. In other words, we sought, as in an experiment, to limit the variables. We limited them, too, not only in this way but also by employing, in history taking, only a few skilled interviewers, each armed with a prescribed set of questions. We made, of course, no frontal attack upon smoking, which in our original questionnaire formed but one section out of nine — eleven questions out of nearly fifty.

Having admitted to a questionnaire of that magnitude I shall take this opportunity to defend myself. For I have been reported as having advocated, before a conference on the application of scientific methods to industrial and service medicine, "that nobody should be subjected to more than five questions."[7] I am, indeed, in favor of shorter and brighter forms but not always to that extent. What I said on that occasion about the problems of making observations of any value, was this: "broadly speaking, of any twenty questions asked in a field survey not more than five should be put to the surveyed, and not less than fifteen should be put to the surveyor by himself before he enters the field or, indeed, ventures to look over the gate."[8] In other words, I maintained, though doubtless somewhat clumsily, that one may ask as many questions as one believes useful — so long as the ratio one to the surveyed and three to the surveyor is maintained throughout. A basic query in the latter group will be, in every case, "is this question really necessary?" It is surprising how often that will effectively keep down the number incorporated.

On the other hand the observational approach has perhaps been somewhat discredited by a too frequent failure to keep down that number, a pathetically notable lack of the critical and imaginative thought that, as Sinclair noted, must be an integral part of the scientific method, — in other words, and more briefly, too few ideas chasing too many forms. That evil is, of course, no prerogative of the United States of America, but I cannot refrain from citing from Eric Linklater's[9] delectable book (that is, to an Englishman) *Juan in America.* Even twenty-two years ago he was moved to write that "the issuing of questionnaires had become a national habit, and work was provided for many people, who might otherwise never have found employment, in dealing with such returns: that is in docketing them, tabulating, copying, indexing, cross-indexing, rearranging them, according to ethnic, religious, social, geographic and other factors, and eventually composing a monograph on them for the Library of Congress." Perhaps Americans were quicker off the mark. I would, however, warn them that we on the other side of the Atlantic are not being backward and may even overtake them in these national vices and devices.

Returning to my theme it is, of course, possible that the relative absence of nonsmokers and the relative frequency of heavy smokers that Doll and I found in our patients with cancer of the lung (and that other workers have also noted) is really a function of some other difference between the two groups. We do not ourselves, for several reasons, believe that to be so, and it is certainly worth noting that patients with pulmonary cancer and controls are remarkably alike in other characteristics that we have recorded. Nevertheless, here lies, I admit, the weakness of the observational as compared with the experimental approach. With the former we can determine the most probable explanation of a contrast in our data; given the provision that we have taken sufficient care to remove disturbing causes, that probability can be very high. But with a well de-

signed experiment it should be possible to eliminate (or allow for) nearly all disturbing causes and thus to render the interpretation of the contrast even more certain.

Yet in this particular problem what experiment can one make? We may subject mice, or other laboratory animals, to such an atmosphere of tobacco smoke that they can — like the old man in the fairy story — neither sleep nor slumber; they can neither breed nor eat. And lung cancers may or may not develop to a significant degree. What then? We may have thus strengthened the evidence, we may even have narrowed the search, but we must, I believe, invariably return to man for the final proof or proofs.

In this instance one other method of inquiry is now being applied both in the United States and the United Kingdom: a "looking-forward" investigation. Up till now investigators have taken already marked subjects — together with a control series — and have inquired into their antecedents. That has been the method not only, of course, in this particular inquiry but in many others. It is a natural approach and one likely to yield quick returns. Adult patients with peptic ulcers are questioned concerning whether they came from broken homes; those with rheumatoid arthritis are questioned on their previous shocks and ills; and the views of the victims of neurosis upon the habits of their fathers are sought. The resulting picture, the contrast between marked and unmarked, may be clear cut, and yet it may be difficult to distinguish between effects and causes, between horse and cart. Memories may well be more profound and more retentive in the "marked," and they may indeed be more highly colored — what the adult neurotic thinks of his father may not always be the truth. Even with the method at its best one can rarely hope to make a prognosis by these means, to measure the probabilities of events. But that is what is usually needed: first to observe the broken, and unbroken, home and then to record the subsequent history of its youthful inmates. That is clearly difficult to do and calls for a considerable degree of patience, which most investigators do not possess. But if the forward approach can be employed, it is, I believe, almost always the right way to go to work; in any observational inquiry its possibility should invariably be considered.

In the particular investigation that Doll and I now have under way — broadly into the deaths in the next few years of men and women on the British medical register whose smoking habits are already characterized at a defined point of time (late 1951) —it again, of course, would not follow that any association we might find between death from carcinoma of the lung (or other causes of death) and smoking habits must be a direct association. The heavy smokers may be differentiated from the light smokers in some other way, which might have some bearing on the risks of a bronchial carcinoma. We are still faced with the most probable explanation. But we may, I submit, have further narrowed the field of possible variables, of errors of omission or commission.

The Field Experiment

There is today an increasing resort to the field experiment, a district, a town, a school or a factory being used as the laboratory. It is a striking development of the present age and, if the requirements of an efficient experiment can be met, a most valuable one. But those requirements *must* be met; a poor experiment serves no purpose. Yet it seems that the very magic in its name may serve to mislead those who worship at the experimental shrine.

As an example, in a recently reported study of vaccination against influenza, the subjects for inoculation were chosen on a voluntary basis and "without any great propaganda 32.8% of the total employees involved in the Survey voluntarily requested the inoculations." This one third, self-selected group is compared with the remaining two thirds, who, like Gallio, "cared for none of those things." Of the 1148 inoculated persons 10.80 per cent were attacked by influenza, and of the 2349 remaining population 15.02 per cent. The difference is "statistically significant" with a "P of 0.00567." And yet does this ritual and do all these decimal places mean anything at all? Admittedly, the technical test says that the two groups had experiences that differed by more than one would expect to occur by chance; equally, it tells nothing else. As it stands I do not myself believe that it gives any support whatever for the author's conclusion that here is evidence "strongly in favor of the immunization of large groups in industry." Yet I have no doubt that it will be cited in the literature under the caption "it has been shown by experiment."

In my view this is not an experiment at all. Some observations have been made of the recorded incidence of "influenza" in two groups. The investigator knew (and so incidentally did the two groups) that they differed in one respect — inoculation; they may well have differed in a score of others — even, for all one is told, in such simple respects as age and sex. None of the other possible variables of importance were controlled, and it is well known that in trials of vaccines a self-selected group is most unlikely to be a representative sample of the total. Field experiments are not, unfortunately, as easy to design and carry out as all that. In this particular field — vaccination against influenza — I speak with conviction, for the Medical Research Council has during the last winter carried out some experiments in industry, — trials of methodology, I should say, as much as of vaccines. We too, of course, have had to rely upon volunteers for our basic material. There is (fortunately) no other way of setting up a trial.

But the volunteers were divided at random into two groups — an inoculated group given the influenza vaccine and an inoculated group given a dummy vaccine. We had their general consent to that procedure, but in the individual case it was unknown. It was also unknown to the medical practitioner diagnosing such illnesses as occurred — influenza, possibly influenza and other diseases. In such ways we have endeavored to equalize our groups *de novo* — to eliminate bias from the subsquent observations. Whether, having to cast our epidemic net wide, we have succeeded in obtaining accurate and comparable records from a score of factories and still more doctors remains to be seen. Such experiments involving human beings are, I repeat, not easy to carry out; they are, as a rule, costly. Yet in relation to the returns rendered they are relatively cheap. A well designed plan may in a few months, or years, forestall years or decades of indeterminate, unplanned observation.

Conclusion

There is one thread that runs — or it might be more accurate to say wanders — through this lecture. I have been unable — even if I would — to conceal my preference in preventive medicine for the experimental approach. At the same time that preference does not lead me to repudiate or even, I hope, to underrate the claims of accurate and designed observations. But I would place all the emphasis at my command upon those adjectives. In this field of preventive medicine I share, on the whole, the view regarding the curative aspects recently expressed by Platt,[10] professor of medicine in the University of Manchester. Records in clinical research are likely, he suggests, to be disappointing;

> Unless they have been kept with an end in view, as part of a planned experiment. . .Clinical experiment need not mean the subjection of patients to uncomfortable procedures of doubtful value or benefit. It means the planning of a line of action and the recording of observations designed to withstand critical analysis and give the answer to a clinical problem. It is an attitude of mind.

In appropriately exploiting that attitude of mind one may well need, in this age of technicalities, close and constant collaboration. Today, as Joseph Garland[11] pointed out in this city of Boston, "the mathematics of research has expressed itself in a multiplicity of graphs, charts and tables with the aid of which the average reader at a quick glance can often learn next to nothing." The biostatistician must therefore acquire a taste for lying down with the epidemiologist, and the bacteriologist with the medical officer of health (I speak in fables).

There are, of course, no grounds for antagonism between experiment and observation. The former, indeed, depends on observation but of a type that has the good fortune to be controlled at the experimenter's will. In the world of public health and preventive medicine each will — or should — constantly react beneficially upon the other. Observation in the field suggests experiment; the experiment leads back to more, and better defined, observations. However that may be, it is difficult to see how one can wholly, or ever, escape from Alexander Pope's epigram. How else but by observation upon man himself being born, living and dying, can one set about the solution of such problems as prematurity and stillbirth at one end of life and cancer and coronary thrombosis at the other? However tangled the skein of causation one must, at least at first, try to unravel it in vivo. As Pickering[12] has said: "Any work which seeks to elucidate the cause of disease, the mechanism of disease, the cure of disease, or the prevention of disease, must begin and end with observations on man, whatever the intermediate steps may be."

The observer may well have to be more patient than the experimenter — awaiting the occurrence of the natural succession of events he desires to study; he may well have to be more imaginative — sensing the correlations that lie below the surface of his observations; and he may well have to be more logical and less dogmatic — avoiding as the evil eye the fallacy of *post hoc ergo propter hoc*, the mistaking of correlation for causation.

Lastly, I quote the words of Professor William Topley,[13] a British worker for whom I had a profound admiration and from whose wisdom I endeavored to learn:

> A great part of clinical medicine, and of epidemiology, must still be observation. Nature makes the experiments, and we watch and understand them if we can. No one will deny that we should always aim at planned intervention and closer control. Here, as elsewhere, technique — the way we make our observations and check them — is half the battle, but to force experiment and observation into sharply separated categories is almost as dangerous a heresy as the science and art [of medicine] antithesis. It tends to make the clinician in the ward, the epidemiologist in the field, and the laboratory worker at his bench, think of themselves as doing different things, and bound by different rules. Actually they are all making experiments, some good, some bad. It is more difficult to make a good experiment in the ward than in the laboratory, because conditions are more difficult to control; but there is no other way of gaining knowledge... Controlled observation in the ward or in the field is an essential part of medical science, shading through almost imperceptible stages of increasing intervention into the fully developed experimental technique of the laboratory.

Mr. Winston Churchill, revisiting the Niagara Falls after more than forty years, was asked by a reporter "Do they look the same?" "Well", he is said to have replied, "the principle seems the same." General principles are obstinate things; they do tend to remain the same generation after generation. Yet one element of that sameness — their fundamental importance — perhaps justifies their being brought out into the light of day from time to time and, if one cannot weave fresh clothes, at least in a newly

dyed costume. In accepting the honor of delivering this Cutter Lecture I indeed trusted that that was so. If I was wrong I must comfort myself like that charming character described by Anatole France: like Monsieur Bonnard, I have the satisfaction of believing that, in following my distinguished predecessors, I have at least "utilized to their fullest extent those mediocre faculties with which Nature endowed me."

References

1. Sinclair, H. M. Nutritional surveys of population groups. *New Eng. J. Med.* **245**:39-47, 1951.
2. Yule, G. *The Function of Statistical Method in Scientific Investigation.* (Industrial Health Research Board Report.) No. 28. 14 pp. London: His Majesty's Stationery Office, 1924.
3. Greenwood, M. Is statistical method of any value in medical research? *Lancet* **2**:153-158, 1924.
4. Tippett, L. H. C. *Statistics.* 184 pp. London: Oxford University Press, 1943.
5. Lancaster, H. O. Deafness as epidemic disease in Australia: note on census and institutional data. *Brit. M. J.* **2**:1429-1432, 1951.
6. Stocks, P. *Modern Trends in Public Health.* Edited by A. Massey. 591 pp. London: Butterworth, 1949. Chap. XIX.
7. Himsworth, H. P. *The Application of Scientific Methods to Industrial and Service Medicine.* (Medical Research Council.) London: His Majesty's Stationery Office, 1924. P. 107.
8. Hill, A. B. Cited by Himsworth.[7] P. 7.
9. Linklater, E. *Juan in America.* 466 pp. London: Jonathan Cape, 1931.
10. Platt, R. Wisdom is not enough: reflections on art and science of medicine. *Lancet* **2**:977-980, 1952.
11. Garland, J. *New England Journal of Medicine* and Massachusetts Medical Society. *New Eng. J. Med.* **246**:801-806, 1952.
12. Pickering, G. W. Opportunity and universities. *Lancet* **2**:895-898, 1952.
13. Topley, W. W. C. *Authority, Observation and Experiment in Medicine.* 46 pp. London: Cambridge University Press, 1940. P. 40.

NONSYPHILITIC INTERSTITIAL KERATITIS AND BILATERAL DEAFNESS (COGAN'S SYNDROME) ASSOCIATED WITH ESSENTIAL POLYANGITIS (PERIARTERITIS NODOSA)*

A Review of the Syndrome with Consideration of a Possible Pathogenic Mechanism

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CHICAGO

In 1945, Cogan[1] described a syndrome consisting of nonsyphilitic interstitial keratitis with deafness. Subsequently, a number of other cases were reported, mostly in the ophthalmologic literature. Although these authors speculated on an association with systemic disease, no definite etiology could be found in fifteen cases [1-6] reported up to the present. We have had the opportunity of observing an additional case in which two episodes of oculo-aural symptoms occurred before the onset of extensive vascular lesions, pointing to a possible association between essential polyangitis (periarteritis nodosa) and the initial symptoms. In view of the rarity of the syndrome, it may be useful to describe its manifestations as observed.

The syndrome usually occurs in young adults and is of sudden onset, either with ocular or aural symptoms. The presenting ocular symptoms may include redness of the eye, blurring of vision, ocular pain, lacrimation, blepharospasm and subconjunctival hemorrhage, and may involve one or both eyes at the onset. The vestibuloauditory signs, which are similar to those of Ménière's syndrome, appear suddenly, with nausea, vomiting, tinnitus, vertigo and rapid development of deafness. With the onset of deafness, the associated vestibular signs diminish. The symptoms of both systems may occur within a few hours of each other, or there may be an interval up to five months, though in the majority of cases, it is between one and two weeks.

Examination of the eye early reveals a granular type of corneal infiltrate, patchy in distribution, found predominantly in the posterior half of the cornea. The endothelium of the cornea may be boggy. There may be little or no reaction in the anterior chamber or the iris, although cases with iritis, uveitis, and secondary glaucoma have been reported. The cornea usually is not thickened; the retina is not involved. Late in the disease, vascularization of the cornea develops. There may be a sluggish reaction to mydriatics, and there may be extraocular muscle paralyses. The vestibuloauditory signs are those of inner-ear deafness, either unilateral or bilateral, with diminished to absent vestibular responses. The neurologic examination, except for the findings mentioned above, is negative. In 8 cases, leukocytosis was present, and 5 of these were associated with a mild eosinophilia; usually, the eosinophil count was from 5 to 8 per cent, although in 1 patient it ranged up to 28 per cent. The serologic reaction for syphilis is negative, nor is there a history of the infection in either the family or the patient. The cerebrospinal fluid reveals no abnormal findings. Additional clinical facts are noted in Table 1.

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Etiology

In reviewing his 8 cases, Cogan[1] came to the conclusion that the cause of the syndrome was not determined. Rosen[3] considered it an atypical manifestation of postvaccinial encephalitis. Lindsay[6] thought that the syndrome was probably of viral origin.

Table 1. *Clinical Data in 16 Cases of the Syndrome of Keratitis and Deafness.*

Age Range	Sex	Immediate Prior History	Past History	Allergy	Effect of Weather	Additional Physical Findings	Course	Laboratory Data
yr.								
20–38	Predominantly male (10 of 16 cases)	Upper respiratory infection (3 cases); vaccination for smallpox (2 cases); occurrence before menses (1 case); bronchopneumonia (1 case).	"Anemia" (1 case); exposure to lewisite (1 case); "rheumatic fever" (1 case); tooth abscess (1 case).	History (3 cases); drug sensitivity noted during treatment (2 cases).	Ocular flare-up during damp weather (2 cases); ocular flare-up during hot weather (1 case).	Abscessed teeth (3 cases)	Vestibular function almost always lost; hearing recovered, partially or completely, in 4 cases; visual acuity decreased, with keratitic precipitates and corneal vascularization.	Leukocytosis (8 cases); eosinophilia (5 cases).

Course and Prognosis

The syndrome runs a chronic course with multiple, unpredictable recurrences. The onset with ocular symptoms is as common as that with aural symptoms. There may be one acute episode with daily variation of the ocular symptoms in the same eye, or from one eye to the other. Or there may be discrete episodes with remission in between. If vascularization and keratitic precipitates are present, visual acuity may be decreased. With the advent of cortisone in the therapy of eye disorders, ocular sequelae may be minimized. As far as the vestibuloauditory symptoms are concerned, there may be tinnitus and slight vertigo with recurrences, but vestibular function is almost always lost. Although there is rarely any variation in hearing once deafness has occurred, some recovery (partial to complete) in hearing has been noted in 25 per cent of cases.

Treatment

Irrespective of the type of therapy employed, results in general were disheartening. In the acute phase of the disease antibiotics, cortisone and antisyphilitic therapy were of no avail, nor was prolonged intravenous histamine therapy. Sympathectomy performed in 4 cases resulted in slight improvement of hearing in 2.

Case Report

A 23-year-old dietitian, was admitted to the hospital on October 29, 1950, with the chief complaint of vertigo, nausea and vomiting of 1 day's duration. She had felt relatively well until the onset of these symptoms, which began as intermittent nausea about 2 weeks previousiy but which had subsided. There was no history of suspect foods, alcohol or drug intake. There was no recent upper respiratory infection and no history of an ear infection, although there had been a tooth abscess just before admission.

The past history revealed scarlet fever and a tonsillectomy during childhood. There was an allergic history manifested by hay fever during August for the past 8 years and reactions to dog's hair and other substances. The last menstrual period had occurred 4 weeks previously.

Physical examination revealed a woman in no acute distress. Vertigo was produced by motion of the head. First-degree nystagmus was present on both sides, especially the right. The pupils reacted slowly to light. Neurologic examination was otherwise negative. Nontender lymph nodes were palpable in the neck, axillas and left inguinal area. There were no hearing difficulties on gross testing. The symptoms were regarded as representing labyrinthine irritation that was possibly due to vasomotor instability.

The blood pressure was 120/80. The pulse was 78 and regular.

The patient was kept in bed and given intravenous infusions of fluids and nicotinic acid, 100 mg. daily. The symptoms were still acute when, 3 days after admission, she began to menstruate. Two days thereafter she had improved somewhat. One week after admission she complained of tinnitus and a sense of fullness in the left ear. Examination showed the hearing to be decreased especially for whisper. The Weber test was not lateralized. An audiogram demonstrated an average 30-decibel loss in the left ear up to 4096 double vibrations with precipitous loss for higher tones. The diagnosis of Ménière's syndrome was suggested, and daily histamine intravenously was instituted. About 11 days after admission, there was a recurrence of the acute symptoms, with nystagmus. The acute symptoms subsided within a few days. Tests revealed some residual hearing impairment on the left when the patient was discharged on November 18, 1950.

She was readmitted to the hospital about 5 weeks later, on December 24, with a 5-day history of dizziness, bilateral tinnitus, nausea, vomiting and total bilateral deafness of 1 day's duration. In the interim the patient had been seen by another physician for occasional nausea, vertigo and intermittent tearing of the left eye, and had been treated with cortisone eye drops for "keratitis." It became evident that this tearing and redness of the eyes had been present before the first admission. She had had a normal menstrual period in the interim. Physical examination revealed 1st-degree sustained nystagmus to the left, with total loss of hearing to shout bilaterally.

She was placed on a salt-free diet that included potassium chloride, and intravenous injections of histamine were given daily for about 5 weeks. The acute symptoms subsided within a few days, leaving some vertigo on motion and total deafness. Hearing tests were all negative, and there were no responses to caloric stimulation in either ear. About 1 week after admission, she had a normal menstrual period. Within 2 weeks she began to walk without aid, not complaining of vertigo despite vestibular loss. Empirically, cortisone in a dosage of 100 mg. daily was given for 1 week, without any effect on hearing. Repeated hearing and caloric tests revealed total loss of function bilaterally. About 4 weeks after admission, she began to complain of photo-

phobia, inability to focus and inability to keep her eyes open. There were bilateral superficial and interstitial corneal infiltrates. The lesions were deep, yellowish white and nodular. The cornea around these lesions appeared clear and shining. There was little or no iridocyclitis. Neither cells nor beam was seen. Corneal sensitivity was normal. The patient had difficulty in maintaining fixation in the primary position and on upward gaze, and with the red glass, the right inferior oblique appeared to be paretic. The fundi and visual fields were normal. To rule out myasthenia gravis as a cause of the paresis, 1 mg. of prostigmine was given subcutaneously, but no effect was noted on the diplopia or ability to raise the lids. The diagnosis of nonsyphilitic interstitial keratitis with deafness (Cogan's syndrome) was considered. Cortisone and atrophine eyedrops were prescribed for the keratitis and pain. Within 2 weeks there were no ocular symptoms or signs, but there was no evidence of hearing on testing or of vestibular function in either ear. Extensive psychiatric investigation, including interviews conducted under Pentothal narcosis, indicated an organic cause for the symptoms. The patient was discharged on February 12.

In the 6 weeks between the 2nd and 3d admissions,there was an early recurrence of the ocular symptoms. While seen by another physician she was given chloramphenicol eyedrops, and chloramphenicol therapy by mouth. Because the antibiotic failed to control the complaints, cortisone by injection was again given. Thus, about 3 weeks before admission the patient received cortisone daily for 6 days (dosage not specified). About 1 week later, or 1 week before the third admission, she was seen by one of us because of crampy abdominal pain, diarrhea and loss of appetite. Physical examination was negative except for diffuse abdominal tenderness and a purpuric, tender nodule on the outer aspect of the left ankle. The complaints continued and were joined by pain and stiffness of the neck, daily low-grade temperature elevation, ocular pain and photophobia, and stiffness of the left ankle, with pain on walking. The patient began to menstruate just before the third admission.

She was readmitted to the hospital with these complaints on March 24. Physical examination showed her to be in acute distress. There were nontender lymph nodes in the left cervical and right axillary areas. There was a Grade 3 systolic murmur now heard over the precordium, but especially at Erb's point. Generalized abdominal tenderness, mainly in both lower quadrants, was evident. The spleen was not palpable. The lesion of the left ankle was as described above, and there was a maculopapular rash over the left side of the face. Neurologic examination revealed some nuchal rigidity, a suggestive positive Kernig sign, spasm of the right sternocleido-mastoid muscle and the previously reported total deafness.

The temperature was 101°F., and the pulse was 120 and regular; the blood pressure was 110/70.

Examination of the blood disclosed a red-cell count of 4,600,000, with a hemoglobin of 13.1 gm., and a white-cell count of 20,000, with a normal differential. A spinal tap was negative. The serum total protein was 6.9 gm. per 100 cc., with an albumin of 2.7 gm. and a globulin of 4.2 gm. per 100 cc.

The impression was that we were dealing with either lupus erythematosus or a bacteremia with meningitis, in addition to acute keratoconjunctivitis and uveitis.

After blood cultures had been made, penicillin in a dosage of 1,200,000 units daily and chloramphenicol in a dosage of 2 gm. daily were given, in addition to cortisone eyedrops. In spite of antibiotic therapy, daily temperature spikes to 102.6°F. were noted, and the patient continued to complain of crampy abdominal pain and stiffness and pain in the neck. Penicillin, 400,000 units daily, was subsequently given. On the 3rd day a lesion appeared on the right ankle similar to the one on the left. On the following day, the stools became loose and frequent again, and on the fifth day she had a number of bloody stools, which persisted for a few days. After the initial bloody stools, the hemoglobin had dropped to 10.2 gm., and the red-cell count to 3,410,000. The bone marrow at this time was normal, the L. E. (lupus erythematosus) preparation being negative. On March 28, the lesion of the left ankle became fluctuant, red and hemorrhagic and was aspirated. There were also nodose lesions on the arms and legs, asymmetric in distribution, that were red and tender, as well as subcutaneous nodules. On March 30 a pleural friction rub was heard in the left anterior axillary area at the 8th rib, and biopsies of a subcutaneous node, nodose skin lesion, quadriceps muscle and skin from the abscessed ankle area were made. Except for muscle, which showed no histologic changes, all sites demonstrated multiple abscesses with periarteritic changes. It was difficult to decide whether the inflammatory lesion or the vascular lesion was primary. Special stains revealed no bacteria (Fig. 1). A blood culture was reported as showing hemolytic streptococci sensitive to 2.5 Oxford units of penicillin and 4 microgm. of chloramphenicol. It was believed that the patient had a panarteritis due to septicemia, involving the skin, neck, muscle, myocardium, pleura, mucosa of the gastrointestinal tract and mesenteric vessels.*

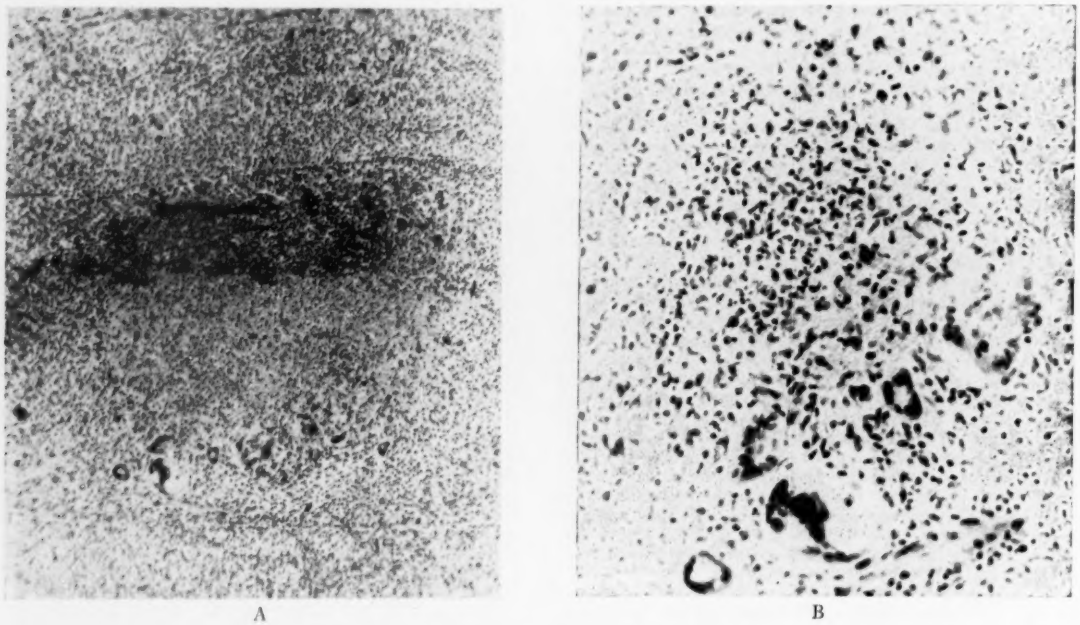
FIGURE 1. *Section from the Initial Biopsy of a Subcutaneous Node, Showing an Abscess Cavity Surrounded by Young Granulation Tissue* (x65).

There is a diffuse adventitial inflammatory infiltrate of the regional vessel that is pleomorphic in character.

On March 31 penicillin in a dosage of 20,000,000 units daily, was given by the intravenous route, followed by 30,000,000 units daily for 3 days. Temperature elevations up to 102.6°F. continued; penicillin was stopped, and administration of chloramphenicol, 2 gm. daily, and dihydrostreptomycin, 1 gm. daily, was started. The patient also received 4 blood transfusions up to this period. Three days later, the temperature was below 99°F. but rose later to hover around 100°F. The bloody stools had stopped. Most of the nodose lesions of the extremities had disappeared. On April 11, red and nontender nodules along the veins on the extensor surfaces of the arms appeared at sites where intravenous infusions of fluid had been given. The heart was enlarged, the border extending to the anterior axillary line, and there was a Grade 1 systolic murmur, with the 1st heart sound split. The spleen was palpated 1 fingerbreadth below the costal margin. The ulcer of the left ankle showed some granu-

*Subacute bacterial endocarditis, with streptococci found in blood cultures, has frequently been associated with essential polyangiitis. This was considered to establish a specific causative agent for the vascular lesions until other bacteria (staphylococci and gonococci) were cultured.[7]

lation tissue. An electrocardiogram at this time was reported as a borderline curve, and the changes between the one taken on admission and this one were nonspecific, but significant; a tracing was some ocular pain, and a few new subcutaneous nodules had appeared on the right wrist. The heart was still enlarged, the border of dullness extending to 3 cm. outside the median clavicular line in the 5th interspace, but no murmurs could be heard. By May 2, there were again low-grade temperature elevations. A biopsy of subcutaneous nodules of the right wrist was reported as showing giant-cell angitis, a variant of periarteritis nodosa (Fig. 2). As a result of the biopsy report, previous medications were discontinued, and ACTH was instituted in a dosage of 25 mg. every 6 hours, for 1 week, with 10,000,000 units of penicillin daily.



A B

FIGURE 2. *Subsequent Biopsy of a Subcutaneous Node.*

A = oblique section through a vessel wall (x65), showing partial occlusion of the lumen by granulation tissue, densely infiltrated with polymorphonuclear leukocytes, macrophages and giant cells (Langhans and foreign-body variety). The media is diffusely infiltrated with inflammatory cells. B = higher-power magnification of the infiltrate and giant cells, as seen in A (x200).

repeated 1 week later, however, was reported to be within normal limits. On April 16, the temperature was normal, and the pulse was 68 and regular. The blood pressure was 112/68. There

TABLE 2. *Pertinent Laboratory Data during the Four Hospital Admissions.*

Admission	Red-Cell Count	White-Cell Count	Differential Count	Sedimentation Rate	Platelets	Bleeding Time	Clotting Time	Tourniquet Test	Blood Kahn Test	Total Protein	Albumin-Globulin Ratio	Serum Electrolytes
	x10⁶	*x10³*		*mm./hr.*	*x10³*	*min.*	*min.*			*gm./100 cc.*		
1st	4.8	8.2	Normal	25	—	—	—	—	Negative	—	—	Normal
2d	4.2	9.6	Normal	38	327	1.5	11.0	Negative	Negative*	7.7	4.7:3.0	Normal
3d	4.6	20.0	Normal	46	—	4.0	11.5	—	Negative	6.9	2.7:4.2	—
4th	4.0	9.4	Normal	42	—	—	—	—	Negative	7.4	3.8:3.6	Normal

*Blood Kahn test of patient's mother also negative.
†Including examination for leptospirosis.
‡Later nonspecific, with increased eosinophils and plasma cells.

On May 13 the ACTH dosage was cut in half, and the patient sat up in a chair. The dosage of ACTH was slowly decreased, and the drug was stopped entirely 5 days later.

The white-cell count was 12,800, with 6 per cent eosinophils. After this, the patient was afebrile and asymptomatic except for

moderate eye symptoms, although stools even at the end of May still showed ++++ guaiac and ++++ Benzidine reactions, which had been reported intermittently before.

On admission the pupils were 3 mm. in size, and reacted to light. Both corneas were hazy, and there was severe ciliary injection. In the upper third of the right cornea there were large, white infiltrates, which were also present on the left but to a lesser extent. On the 4th day a grayish, nodular, granular area about 2 mm. in size appeared in the conjunctiva of the left eye at 12 o'clock near the limbus. On the following day, the nodular lesion was larger, elevated and round. By the 8th day, 2 smaller lesions appeared on either side of the larger lesion, and in the right eye there was a similar lesion at 9 o'clock near the limbus. The original lesion in the left eye had changed, so that the conjunctival swelling had disappeared, and, immediately below this, there appeared a thinning and necrosis of the sclera. The lesion in the right eye progressed in a similar manner. Cortisone, which had been given locally to alleviate pain, was discontinued because of the possibility that it would delay healing and spread infection.

By April, a 2-mm., scleral lesion remained in the right eye; it appeared punched out and partially perforating.In the left eye there were 2 completely perforating lesions at 12 o'clock (Fig. 3). The cornea showed numerous spotty, gray stromal lesions in the upper half. The bulbi were markedly injected.

The condition of the eyes remained the same until 1 month later, when radial thinning of the sclera was seen concentric with the limbus from 11 to 1 o'clock, reaching 6 mm. from the limbus in both eyes. The ulcerated areas had healed over by this time.

The patient was discharged on June 19, totally deaf and with moderate eye symptoms.

She was readmitted to the hospital on July 5, 2 weeks after discharge, with the complaints of photophobia, lacrimation and inability to hold her lids up, of 5 days' duration. She stated that 1 day before the present flare-up she had been exposed to a cat at home. About 1 year previously she had reacted with swelling of eyelids and lacrimation when exposed to a dog. Examination revealed deep interstitial corneal infiltrates, to which superficial and deep vessels led. The pupils reacted sluggishly to light. The sclera was thinned, and there was diffuse episcleral injection. In addition, excessive lacrimation and photophobia were noted. The remaining examination was negative except for the healing ulcers over the malleoli of the ankles. The temperature was 98.4°F., and the pulse 84. The patient was given Benadryl, 150 mg. daily, cortisone and atropine eyedrops and chloramphenicol ophthalmic ointment. Six days later there was minimal lacrimation and photophobia, and minimal ciliary flush, although the infiltrates were still present. Thirteen days after admission she was discharged, with faint corneal infiltrates still present, to continue cortisone eyedrops at home.

Laboratory data during the 4 admissions are presented in Table 2.

Discussion

The cause for the syndrome of nonsyphilitic interstitial keratitis with vestibuloauditory symptoms has not been established in the 15 hitherto published cases. Other syndromes involving the eye and ear were reviewed for a clue to the cause, but the etiology was not established in most of them (Table 3).

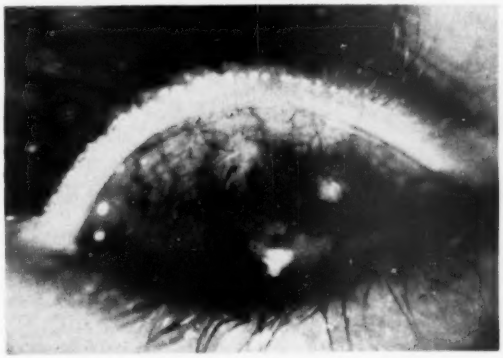


Figure 3. *Appearance of the Left Eye in April, 1951, Showing Punched-Out Ulcerations of the Upper Sclera and Marked Conjunctival Injection.*

The case presented above had all the features of the syndrome mentioned by Cogan,[1] but it is unique in that after two acute episodes the clinical picture of essential polyangitis developed (periarteritis nodosa), with involvement of the gastrointestinal tract, skin, heart, pleura and sclera, and a flare-up of the keratitis occurred. Although the occurrence of the syndrome and the subsequent generalized vascular reaction may have been fortuitous, a number of factors support the assumption for a causal relation.

Table 2 (*Concluded*).

Admission	Bacterial and Viral Agglutinations	Spinal Fluid	Blood Culture	Urine	Urine Culture	Bone Marrow	L. E. Test	X-ray Examination	Skin Tests	Electroencephalogram
1st	Negative	Normal	—	Normal	Hemolytic *Staph. albus*	—	—	Chest, mastoids and petrous apexes normal	—	—
2nd	Negative (twice†)	Normal	—	Normal	Hemolytic streptococcus	—	—	Chest, mastoids, petrous apexes and base of skull normal	Purified protein derivative (1st and 2d strength) negative	Abnormal, slow discharge from left occipitoparietal area
3d	Negative	Normal	Hemolytic streptococcus	Normal	Hemolytic streptococcus	Normal‡	Negative	Chest, cervical spine and teeth normal	—	—
4th	Negative	—	—	Normal	—	—	—	—	—	—

In the year since her last admission she has been relatively well, gaining about 15 pounds. In January, 1952, the white corneal opacities were still present. The scleras were thinned so that the choroid could be seen. In March hearing and caloric tests showed bilateral deafness and loss of vestibular function.

In 3 previously reported cases, there was evidence of more generalized involvement than the eye and ear. A two-year history, which began with "rheumatic fever" followed by myositis, extensive weight loss and upper respiratory infection just before the syndrome, was noted in one case.[1] There was a leukocytosis and an eosinophilia, and the patient had a sensitivity reaction to penicillin. The diagnosis of trichinosis was considered, but muscle biopsy failed to support this. The generalized illness may well have been polyangitis, which the negative muscle biopsy does not necessarily rule out. In another case[6] the syndrome developed, and within a few months the patient complained of palpitations and chest pain followed by hemoptysis; no other clinical or laboratory data were noted in the report. Cardiorespiratory symptoms in polyangitis have been reported in about 50 per cent of cases.[15] In another case,[5] generalized organic cerebral damage, substantiated by an electroencephalogram, was apparent; convulsive episodes were associated with the syndrome. Central-nervous-system involvement by polyangitis has been estimated in about 26 per cent of cases, with convulsions occurring in 11 per cent.[15] Although involvement of multiple organs is more common, isolated involvement of the central nervous system may occur.[16]

The other cases of the syndrome reported may not have been followed long enough for development of generalized symptoms, or the ocular and aural symptoms may have been the only localized manifestations of the disease. In addition, a number of common features in both polyangitis and the syndrome support the theory of a single cause. Both are preceded by a history of upper respiratory infections or "rheumatic disease," or may follow vaccination for smallpox.[17] There is a history of allergy present in a fifth of the cases of polyangitis[15]; this was present in 2 of the cases of the syndrome. Leukocytosis and eosinophilia may be present in both conditions.

Ocular involvement with polyangitis occurs in about 23 per cent of cases.[15] Almost all tissues may be involved,[18] some even being silent clinically.[19] Among the more frequent occurrences are hypertensive retinopathy and uveal arteritis (including the long posterior ciliary artery), whereas involvement of arteries of the extraocular muscles, scleritis and keratitis are rare.[20] Keratitis and necrotizing nodular scleritis, as in the case presented above, have been reported. To account for the eye signs in this syndrome, involvement of the long posterior ciliary artery must occur,[22] although direct involvement of the substantia propria of the cornea, since it is mainly collagenous tissue, may also account for the interstitial keratitis. The anterior ciliary arteries may also be involved to give rise to the extraocular muscle palsies, and the subsequent scleritis seen in the case reported above.

Ear involvement with polyangitis is rare, nerve deafness being reported in 3 per cent of cases with neurologic involvement.[23] Since the blood supply of the membranous part of the inner ear is an end circulation, like that of the sclera and that supplying the cornea, any involvement will be noted acutely. Thus, there are changes in sound perception and tinnitus if the cochlear branch is involved, and vertigo, nausea and vomiting if the vestibular supply is interfered with.[24] To account for the deafness and entire loss of vestibular function in this syndrome, the internal auditory artery must be involved. Recently a case of polyangitis with bilateral deafness was reported[25] in which histologic examination of the eighth cranial nerve demonstrated loss of myelin and fragmentation and varicosities of the axis cylinders. These changes were regarded as resulting from ischemia.

Essential polyangitis is the name given to a group of entities with diffuse vascular involvement, presenting varying clinical and pathological pictures. Clinically, the general picture may be predominantly that of a nonspecific subacute or chronic febrile wasting illness; an atypical abdominal illness of similar duration; a primary renal disease; or a combination of polyneuritis and polymyositis.[7] Cranial arteritis[26] and the Loeffler syndrome[7] are considered to be localized manifestations of polyangitis, although the former has

TABLE 3. *Syndromes Involving the Eye and Ear and Their Possible Etiology.*

SYNDROME	MANIFESTATIONS	ETIOLOGY
Vogt-Kayanagi	Uveitis, alopecia, poliosis, vitiligo and deafness	(?) Viral
Harada	Choroiditis or uveitis, retinal detachment, vitiligo, poliosis and possibly deafness	(?) Viral (1 case due to sarcoidosis)[9] — Now considered to be the same syndr.
Sympathetic ophthalmia	Uveitis after trauma to other eye — rarely, also, retinal detachment, keratitis, scleral nodules, poliosis and deafness	Considered to be infection (viral) as well as sensitization to uveal pigment[10]
Ménière	Deafness and vestibular dysfunction; possibly associated diplopia,[11] glaucoma[11, 12] or iritis.[14]	(?) Vasomotor instability
Interstitial keratitis with deafness	Interstitial keratitis, with vestibuloauditory symptoms; possibly, also, uveitis, glaucoma and extraocular muscle palsies.	Localized manifestations of essential polyangitis

[9]Sarcoidosis with uveitis and involvement of hearing and vestibular function has been reported.[9]

been classified as a separate entity on histologic grounds by some authors.[27] The syndrome of interstitial keratitis and deafness is added to the localized manifestations. Pathologically, it may vary from minimal perivascular lymphocytic infiltration to necrotic panvasculitis and granuloma formation with giant cells.[28] There may also be extravascular lesions in the myocardium, in the skin (abscess formation) and the cornea (keratitis).[28, 29] In the case reported above, two of the pathological manifestations were noted: the abscess formation with periarteritis changes in the initial biopsy, and subsequent appearance of giant cells with granuloma formation.

As far back as 1926, Gruber[30] observed that polyangitis was not a disease caused by a specific agent but the end result in patients with increased sensitivity of the vascular system to nonspecific agents, including streptococcal infection, syphilis and drugs (iodine,[31] penicillin[32, 33] and propylthiouracil[34, 35]), which have been implicated as causes. Rich[36] considered "hypersensitivity" reactions responsible. Smith and Zeek,[37] on the basis of experimental evidence, disputed whether hypersensitivity alone was responsible for the lesions. Since a specific cryoglobulin has been reported in polyangitis,[38] we regard polyangitis as the end result of the following simplified sequence of events: a nonspecific antigenic or injurious agent, production of a specific abnormal globulin, associated with mechanical stress, or sustained local hydrostatic pressure[37, 39, 40] resulting in vascular lesions.

The following observations in the case reported above bear comment: the infectious agents in the teeth before the onset of the syndrome, in the urine throughout three admissions and in the blood during the generalized vascular reaction, especially since on two admissions the organisms in the urine and later in the blood were the same (hemolytic streptococci); the role of the cortisone given just before the third admission; and the occurrence of the first and second episodes of the syndrome and the polyangitis just before menses.

The infectious agents in the teeth and urinary tract, especially the hemolytic streptococci, may have been the initial injurious or sensitizing agent since this was the most frequently cultured organism in polyangitis.[41] Cortisone is known to cause spread of infection and thus may have been responsible for the dissemination of the organisms from the teeth and urinary tract to the blood stream. Cortisone is also known to decrease clotting time[42] and, in addition, when given to patients with polyangitis may produce fibrinoid occlusions with infarctions of involved organs, although the perivascular lesions are healed.[43, 44] Whether multiple thrombi were produced just before the third admission or whether fibrinoid occlusion of previous silently involved vessels resulted in the generalized reaction is open to debate.

The occurrence of two episodes of the syndrome and the polyangitis just before the menses may have been a fortuitous relation; on the other hand, endogenous steroids secreted during the second half of the menstrual cycle (estrogen and progesterone) may have been responsible. Sensitivity to estrogens has been reported,[45] but no studies were made on our patient, so that the relation is open to speculation.

The absence of signs of renal involvement was observed in cases of polyangitis, which gave a favorable prognosis.[46] The patient described above apparently also recovered and did not exhibit signs of a major renal lesion during any stage of the disease.

Summary

A unique case of the syndrome of nonsyphilitic interstitial keratitis with deafness (Cogan's syndrome) associated with essential polyangitis (periarteritis nodosa) is presented. The occurrence of the generalized vascular reactions after two episodes of the oculoaural symptoms suggests a causal relation between the two entities. Arguments that the syndrome is only a localized manifestation of essential polyangitis are discussed.

References

1. Cogan, D. G. Syndrome of nonsyphilitic interstitial keratitis with vestibuloauditory symptoms. *Arch. Ophth.* **33**:144-149, 1945. *Ibid.* **42**:42-49, 1949.
2. Morgan, R. F., and Baumgartner, C. J. Ménière's disease complicated by recurrent interstitial keratitis: excellent results following cervical ganglionectomy. *West. J. Surg.* **42**: 628-631, 1934.
3. Rosen, E. Interstitial keratitis and vestibuloauditory symptoms following vaccination. *Arch. Ophth.* **41**:24-31, 1949.
4. Robson, J. T. Cervical sympathectomy in nonsyphilitic interstitial keratitis with vestibuloauditory symptoms. *Arch. Ophth.* **44**:243, 1950.
5. Donald, R. A., and Gardner, W. J. Keratitis with deafness. *Am. J. Ophth.* **33**:889-892, 1950.
6. Lindsay, J. R., and Zuidema, J. Inner ear deafness of sudden onset. *Laryngoscope* **60**:238-263, 1950.
7. Miller, H. G., and Daley, R. Clinical aspects of polyarteritis nodosa. *Quart. J. Med.* **39**(N.S.):255-283, 1946.
8. Walsh, F. B. *Clinical Neuro-Opthalmology*. 384 pp. Baltimore: Williams & Wilkins, 1947. P. 555.
9. Hedges, T. R., and Taylor, G. W. Uveal and vestibuloauditory disease with sarcoid. *Arch. Ophth.* **48**:88, 1952.
10. Duke-Elder, W. S. *Textbook of Ophthalmology*. Vol. 3. 1073 pp. St. Louis: Mosby, 1941.
11. Dandy, W. E. Ménière's disease: its diagnosis and treatment. *South. M. J.* **30**:621-623, 1937.
12. Godtfredsen, E. Concurrence of glaucoma and Ménière's disease. *Acta oto-laryng.* **37**:533-538, 1949.
13. McGrath, H. Ménière's disease associated with traumatic hyphemia and glaucoma. *Am. J. Ophth.* **34**:241-245, 1952.
14. Granstrom, K. C., and Nylén, C. O. Crises de vertige de Ménière et crises d'iritis avec oeuème de Quincke dans les paupières chez une même patiente. *Acta oto-laryng.* **26**:717-725, 1938.
15. Logue, R. B., and Mullins, F. Polyarteritis nodosa: report of 11 cases with review of recent literature. *Ann. Int. Med.* **24**:11-26, 1946.
16. Kernohan, J. W., and Woltman, H. W. Periarteritis nodosa: clinicopathologic study with special reference to nervous system. *Arch. Neurol. & Psychiat.* **39**:655-686, 1938.
17. Ingalls, R. B. Bilateral uveitis and keratitis accompanying periarteritis nodosa. *Tr. Am. Acad. Ophth.* **56**:630, 1951.

18. Hollenhorst, R. W., and Henderson, J. W. Ocular manifestations of diffuse collagen diseases. *Am. J. M. Sc.* **221**:211-222, 1951.
19. Tertsch, R. Ein weiterer Fall von Periarteriitis nodosa mit Veränderungen an den Arterien der äusseren Augenmuskeln. *Ztschr. f. Augenh.* **87**:294-298, 1935.
20. Wise, G. N. Ocular periarteritis nodosa. *Arch. Ophth.* **48**:1-11, 1952.
21. Harbert, F., and McPherson, S. D. Scleral necrosis in periarteritis nodosa. *Am. J. Ophth.* **30**:727-732, 1947.
22. Kohra, T. Cited by Süllmann, H. Biochemie des Auges. *Ophthalmologica* **96**:37-64, 1938.
23. Foster, D. B., and Malamud, N. Periarteritis nodosa: clinicopathologic report with special reference to central nervous system: preliminary report. *Univ. Hosp. Bull., Ann Arbor* **7**:102-104, 1941.
24. Hilger, J. A. Vasomotor labyrinthine ischemia. *Ann. Otol. Rhin. & Laryng.* **59**:1102-1116, 1950.
25. McNeil, N. F., Berke, M., and Rheingold, I. M. Polyarteritis nodosa causing deafness in adult: report of case with special reference to concepts about disease. *Ann. Int. Med.* **37**:1253-1267, 1952.
26. Anderson, W. A. D. *Synopsis of Pathology.* Second edition. 741 pp. St. Louis: Mosby, 1948. P. 584.
27. Wright, I. S. *Vascular Disease in Clinical Practice.* Second edition. 552 pp. Chicago: Year Book Publishers, 1952. P. 264.
28. Clark, W. S. Case Records of the Massachusetts General Hospital (Case 38341). *New Eng. J. Med.* **247**:292-294, 1952.
29. Grant, R. T. Observations on periarteritis nodosa. *Clin. Sc.* **4**: 245-275, 1940.
30. Gruber, G. B. Kasuistik und Kritik der Periarteriitis nodosa. *Zentralbl. f. Herz.-u. Gefässkr.* **18**:145-158, 1926.
31. Rich, A. R. Hypersensitivity to iodine as cause of periarteritis nodosa. *Bull. Johns Hopkins Hosp.* **77**:43-48, 1945.
32. Adelson, L. Periarteritis nodosa in infancy: report of case following allergic reactions to penicillin. *J. Pediat.* **39**:346-353, 1951.
33. Berne, R. M. Unusual sensitivity reaction to penicillin: report of case with autopsy findings. *New Eng. J. Med.* **242**:814-817, 1950.
34. McCormick, R. V. Periarteritis occurring during propylthiouracil therapy. *J.A.M.A.* **144**:1453, 1950.
35. Barnum, D. R., de Takats, G., and Dolkart, R. E. Periarteritis nodosa following thiouracil therapy of hyperthyroidism: resultant hypertension benefited by sympathectomy. *Angiology* **2**:256-262, 1951.
36. Rich, A. R. Role of hypersensitivity in periarteritis nodosa as indicated by 7 cases developing during serum sickness and sulfonamide therapy. *Bull. Johns Hopkins Hosp.* **71**:123-140, 1942.
37. Smith, C. C., and Zeek, P. M. Studies on periarteritis nodosa. II. Role of various factors in etiology of periarteritis nodosa in experimental animals. *Am. J. Path.* **23**:147-157, 1947.
38. Lepow, H., Rubenstein, L., Woll, F., and Greisman, H. Spontaneously precipitable protein in human sera, with particular reference to diagnosis of polyarteritis nodosa. *Am. J. Med.* **7**:310-316, 1949.
39. Old, J. W., and Russel, W. O. Necrotizing pulmonary arteritis occurring with congenital heart disease (Eisenmenger complex): report of case with necropsy. *Am. J. Path.* **26**:789-805, 1950.
40. Kipkie, G. F., and Johnson, D. S. Possible pathogenic mechanisms responsible for human periarteritis nodosa as suggested by occurrence of 2 instances of this disease in association with glomerulonephritis. *Arch. Path.* **51**:387-392, 1951.
41. Spiegel, R. Clinical aspects of periarteritis nodosa. *Arch. Int. Med.* **58**:993-1040, 1936.
42. Cosgriff, S. W., Diefenbach, A. F., and Vogt, W. Jr. Hypercoagulability of blood associated with ACTH and cortisone therapy. *Am. J. Med.* **9**:752-756, 1950.
43. Shick, R. M., Baggenstoss, A. H., and Polley, H. F. Effects of cortisone and ACTH on periarteritis nodosa and cranial arteritis: preliminary report. *Proc. Staff. Meet., Mayo Clin.* **25**:135, 1950.
44. Drury, M. I., Hickey, M. D., and Malone, J. P. Case of polyarteritis nodosa treated with cortisone. *Brit. M. J.* **2**:1487-1489, 1951.
45. Watson, C. J., Schultz, A. L., and Wikoff, H. M. Purpura following estrogen therapy, with particular reference to hypersensitivity to (diethyl) stilbesterol and with note on possible relationship of purpura to endogenous estrogens. *J. Lab. & Clin. Med.* **32**:606-617, 1947.
46. Harris, A. W. Lynch, G. W., and O'Hare, J. P. Periarteritis nodosa. *Arch. Int. Med.* **63**:1163-1182, 1939.

THE PROGNOSIS IN GASTRIC ULCER TREATED CONSERVATIVELY*

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THERE is general agreement that the management of a gastric ulcer is a more exacting task than that of a duodenal ulcer because of the implications of carcinoma masquerading as an innocent gastric ulcer or arising as a complication. The controversial question of carcinomatous degeneration of a benign gastric ulcer versus the theory of ulcerating carcinoma in situ as advocated by Mallory[1] is not discussed in this paper. The more immediate concern is the fact that approximately 10 per cent of gastric ulcers are discovered sooner or later to be cancerous.[2-4] In an attempt to attack so grave a lesion as gastric carcinoma as early and vigorously as possible, a number of surgeons have advocated prompt resection of gastric ulcers.[5] Others, mindful of the mortality of gastric resection, have preferred to treat gastric ulcer conservatively but with appropriate safeguards.[4]

The commonly accepted criteria for differentiating the benign and the malignant ulcer — honored more often in the lecture room than at the bedside — include prompt subsidence of ulcer symptoms under treatment, presence of free hydrochloric acid in the stomach, consistent absence of occult blood from the stools, satisfactory gain in weight, complete disappearance of the ulcer niche on roentgenologic observation within six to eight weeks, and a full return of pliability in the gastric wall at the involved site. In selected cases the information derived from gastroscopic study and from the staining of gastric washings by the Papanicolaou technic may be of value. To these procedures and principles should be added the further surety of uninterrupted medical supervision for at least five years, including periodic x-ray examinations of the stomach even in the absence of clinical symptoms. Since these clinical criteria yield presumptive rather than definitive information, a significant percentage of diagnostic errors is inevitable.[6]

This report is concerned with the clinical course and the late results of the medical management of gastric ulcer in a group of patients treated initially in an urban hospital. The patients were attended in the hospital by a number of physicians either as individual private patients or on the teaching ward service. Their management after discharge was carried on under the guidance of their own doctors

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or in the outpatient clinics of the hospital. It is believed that the treatment of these cases under such diverse conditions reflects the results to be expected in the community at large, where theories of optimal management often give way before such realistic considerations as the unwelcome cost and restrictions of a prolonged medical regimen, the ignorance or inertia of the patient and the unwarranted complacency of the physician.

Procedure

The house and outpatient records of all patients with gastric ulcer admitted to the Medical Service of the Beth Israel Hospital between 1931 and 1946 were reviewed. The records of patients transferred to the Surgical Service and operated on because of complications or suspicion of malignant degeneration were discarded from the survey. The patients considered suitable for inclusion in this analysis on the basis of adequate clinical data, radiologic evidence of ulcer and appropriate medical therapy were recalled to the hospital for a personal interview and physical examination and for repeated laboratory and x-ray observations. When this was not feasible, the necessary information was obtained from hospital records elsewhere or from the office records of their private physicians. When death had supervened, the diagnoses were obtained from surgical or autopsy records or from the death certificates. No case was included in which the follow-up data were not derived from objective professional sources and properly documented.

The resultant series of 48 cases represents a comparatively small portion of all the cases reviewed, but in view of the rigid criteria for their selection the findings may have increased significance. Four patients have been followed for more than fifteen years, 7 for ten to fifteen years, 20 for five to ten years, and the remainder for an average of two and a half years.

Results

There were 34 male and 14 female patients in the group. The youngest was a seven-year-old girl, and 4 patients were more than seventy years of age. Thirty-six were more than fifty years of age when first seen. The duration of symptoms was less than two years in 16 cases, two to five years in 14 cases and more than five years in 16 other cases. In 2 cases the duration of symptoms before hospitalization was not recorded. The incidence of important clinical manifestations and the chief complaint on admission are shown in Table 1. It will be noted that a typical ulcer sequence of pain with relief by food or antacids was present in 34 and that massive internal bleeding had occurred in 17 of the 48 cases. Weight loss and vomiting were not important presenting symptoms. In 4 cases the complete picture of typical ulcer pain, massive bleeding, weight loss and vomiting was present on admission to the hospital.

The location and size of the gastric ulcers are shown in Figure 1. The pathology can be considered representative in that 13 of the ulcers were situated

Table 1. *Analysis of Symptoms in 48 Cases before Hospitalization.*

Symptom	Important Manifestation*	Chief Complaint*
	No. of cases	No. of cases
Typical ulcer sequence	34	31
Atypical pain	9	7
Massive bleeding	17	5
Weight loss	9	0
Vomiting	8	1

*4 patients presented all the symptoms listed.

in the lower third of the stomach, 17 in the middle third, and 17 in the upper third. In 1 case there were multiple ulcers. Nine of the gastric ulcers measured more than 2.5 cm. in size. In 7 cases there was

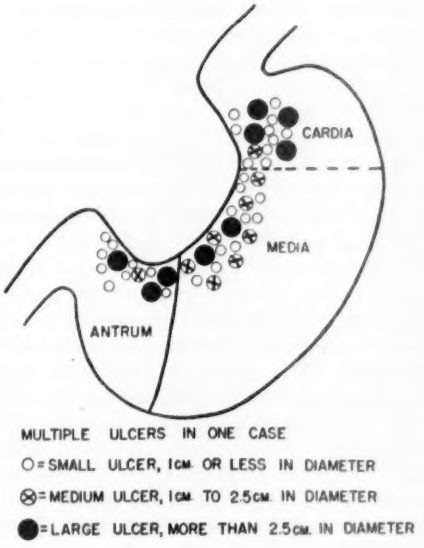
CARDIA
MEDIA
ANTRUM
MULTIPLE ULCERS IN ONE CASE
○=SMALL ULCER, 1cm. OR LESS IN DIAMETER
⊗=MEDIUM ULCER, 1cm. TO 2.5cm. IN DIAMETER
●=LARGE ULCER, MORE THAN 2.5cm. IN DIAMETER

Figure 1. *Approximate Location and Size of Ulcer.*

definite radiologic evidence of an associated duodenal ulcer.

Only 6 cases gave evidence of anemia; in 5 of these, recent or concurrent gross bleeding was responsible. Stools were positive for occult blood (guaiac test) to a significant degree in only 5 cases. The range of gastric acidity, both free and total, varied from low to very high, the level of free acid exceeding 50 units in 9 cases. In 2 cases no free acid was reported on examination, and both ran a benign course.

Gastroscopy was done by various observers in 14 cases, and the ulcer was visualized in 10. The lesion seen was called benign correctly in all but 1 case, which later proved to be a malignant ulcer.

Careful review of the hospital records led to the opinion that three fifths of the patients had received optimal management in terms of length of stay in hospital, amount of rest, regulation of diet, administration of appropriate medications, laboratory control and serial x-ray studies. Other therapeutic factors no less important, such as education and indoctrination of the patient, superficial psychotherapy, and economic or social adjustments, were less susceptible to critical analysis. In the remaining cases there was a tendency to discharge the patient from the hospital prematurely before the adequacy of healing had been fully established. For example, in many of these cases the radiologic findings in the stomach were not rechecked before discharge. The implications of such a defect in management seem obvious in a disease as treacherous as gastric ulcer. Of the patients given serial x-ray examinations during treatment in the hospital there was no change in the size of the lesion in 4; the remainder showed a significant decrease in size or complete disappearance of the ulcer. Two of the four patients in whom x-ray examination failed to give satisfactory evidence of progressive healing died of carcinoma of the stomach one year and sixteen years later, respectively; 1 patient had a single recurrence twelve years later but was alive and well after an interval of seventeen years, and another had frequent reactivations, with repeated hematemeses, and died eight years later of cardiovascular disease.

In half the cases all symptoms promptly disappeared within the first week of treatment in the hospital. In the remainder progress was slow and irregular or was not recorded in sufficient detail for analysis. The repeated testing of stools for occult blood was of only limited value in determining the course and effectiveness of therapy. In three fourths of the cases the stools were consistently free of occult blood throughout hospitalization, and in only 5 did they show more than a slight trace. As might have been expected from the preponderant age groups in this series of patients, the associated diseases comprised mostly cardiovascular and pulmonary disorders, which did not apparently affect the clinical course of the gastric ulcer although the patients constituted a prohibitive surgical risk in several cases.

Of the 48 patients only 11 remained free of ulcer symptoms throughout the follow-up period. An additional 7 have remained well to date after one or more recurrences of ulcer activity, and 2 patients listed as well died subsequently of unrelated causes. Twenty patients continued to have periodic exacerbations of ulcer symptoms; 6 of these eventually submitted to operation. Four others similarly advised have thus far refused operation. Eight patients of the original group of 48 have died of verified carcinoma of the stomach.

Discussion

The results in these cases of gastric ulcer treated conservatively lead to the distinct impression that the outlook for the patient with such a lesion is far from favorable. It must be emphasized that the decision to employ medical management in these cases was based on supposedly reassuring clinical features so that these patients must initially have been considered as preferred risks. During the same period of 1931–1946 68 patients with benign gastric ulcer were treated surgically at the Beth Israel Hospital for various indications, including massive bleeding, acute perforation and intractability. This figure does not include the cases considered preoperatively to be benign that proved at operation to be carcinomatous ulcer and are so classified. Reports from other sources indicate that 13 to 19.8 per cent of patients thus operated on for an ulcer originally presumed to be benign are found to have a carcinomatous lesion.[5, 7] In the remaining select and ostensibly preferred-risk group, upon which this report is based, only 1 of 4 patients remained symptom free over the years, 1 of 6 died of carcinoma of the stomach, and 1 of 5 was operated on or refused operation despite the most urgent indications. With the passing of time it appears probable that these figures will be revised to even less encouraging ratios in that more patients will be forced to accept operation, and some may eventually be found to have a gastric carcinoma.

Of the 20 patients classified as well it is noteworthy that within five years of discharge from the hospital 7 had already experienced one or more symptomatic recurrences confirmed by x-ray examination. In each case the gastric ulcer was in the identical location previously reported. These 7 patients had continued to be symptom free to the date of this survey. It is probable, therefore, that in time 1 or more cases of late recurrent gastric ulcer will appear in this subgroup of 20 patients now classified as well. Smith and Jordan[4] reported a recurrence rate of 47 per cent in 111 cases followed for five years or longer. In a review of 101 patients with gastric ulcer followed for an average period of five and six-tenths years Flood and Hennig[8] found that all except 2 suffered recurrences of clinical symptoms although in only 70 per cent was a recurrent gastric ulcer demonstrated radiologically.

Among the 20 patients classified as actively symptomatic over the years there were no clinical features such as age, sex, duration or nature of symptoms, location or size of lesion, level of gastric acidity, length of stay in hospital, rate of clinical improvement or rapidity of involution of ulcer observed radiologically that would differentiate these cases from those with the more favorable subsequent course already mentioned. This is in keep-

ing with the experience of others.[4, 8] In this active group there were 6 patients with an associated duodenal ulcer known or discovered at the time of initial hospitalization. Another patient manifested an active duodenal ulcer during the follow-up period. For comparison, only 2 patients classified as well had radiologic evidence of duodenal ulcer.

It is worthy of note that in all but 3 of these recurrently active cases, with or without an associated duodenal deformity, an ulcer was again demonstrated in the same area of the stomach, regardless of the interval since the previous attack. In 1 case the recurrent ulcer was in a different segment of the stomach, and in 2 it was not visualized radiologically although the clinical symptoms were considered typical of active ulcer. Others have commented on the frequent failure of x-ray examination to reveal the gastric lesion in patients with recurrent symptoms. The reverse situation also occurs. One patient in this series was asymptomatic in recent years, and yet the same large, silent, ulcerating gastric lesion was demonstrated on repeated x-ray studies during a five-year period. In a series of 101 cases of gastric ulcer reported by Flood and Hennig[8] an active crater was seen on x-ray examination on 6 occasions in patients who had had no recent symptoms of ulcer.

With few exceptions the clinical manifestations of recurrent gastric ulcer were exceedingly severe and characterized by intractable pain, nocturnal distress, vomiting or bleeding. In the group of 20 cases classified as active there were 7 in which serious internal hemorrhage developed after discharge from the hospital. In the entire series of 48 cases hematemesis or melena occurred in 21 at some time before hospitalization or during the follow-up period. Palmer[9] noted the propensity to serious complications in benign gastric ulcer and found that hemorrhage occurred in 30 per cent and perforation in 12 per cent of his cases. Welch and Allen[10] reported the incidence of massive hemorrhage as only 9 per cent and that of obstruction as 1.2 per cent. In the series of Smith and Jordan[4] hemorrhage occurred in 26 per cent, obstruction in 20 per cent, and perforation in 7 per cent. In our 20 active cases 6 patients were operated on at an average of five years after the original period of hospitalization. The indications for operation were repeated hemorrhages in 4 cases, suspicion of carcinoma in 1 case, and intractability of pain in 1 case. In addition 4 patients refused operation, which had been repeatedly and urgently recommended. The remaining 10 patients (including 4 who had died meanwhile of unrelated causes) all had sufficient indications for surgical treatment. In other surveys of gastric ulcer treated medically, the over-all incidence of subsequent operative intervention has varied from 10 to 23 per cent.[8, 11]

Review of the 8 patients who eventually died of carcinoma of the stomach indicates that with the exception of 1 patient in his forties all were more than fifty years of age when first seen. Seven patients gave a classic history of ulcer. In all cases the duration of digestive symptoms before initial hospitalization was more suggestive of a benign lesion. Two patients had complained for two years; the others had suffered for three, five, eleven, sixteen, eighteen and twenty years respectively. In 5 cases the lesion was situated in the upper third of the stomach just below or in the cardia. The size of the lesion varied considerably; in 1 case three distinct gastric ulcers were described. There was radiologic evidence of an associated duodenal ulcer in only 1 case. The gastric acidity varied from very low to extremely high levels, and there were no known cases of achlorhydria. Symptoms subsided within a few days of initiation of treatment in 5 cases, and gradually in 2 cases. One patient had symptoms intermittently. Serial x-ray studies in the hospital showed marked healing of the lesion in 2, complete healing in 1, and no change in 2 cases; in the remainder re-examination was not done, but all these patients had a prompt and completely favorable clinical response to treatment. The gastroscopic diagnosis was benign ulcer in 1 case and hypertrophic gastritis in another.

None of the clinical or laboratory features of these cases before hospitalization gave any reliable intimation of the serious outcome. A favorable clinical course in the hospital also proved to be an unreliable guarantee of safety. Allen and Welch[10, 12] have found similarly that the usual clinical indexes are of equivocal value in the differentiation of benign and malignant ulcer. Occasionally, a carcinomatous ulcer appears to heal rapidly, whereas a benign ulcer may heal slowly, especially in the aged. According to Flood and Hennig[8] 4 of 5 patients with medically treated gastric ulcer who were later found to have carcinoma of the stomach demonstrated initially complete disappearance of the gastric lesion on serial x-ray examinations. On the basis of anatomic studies in 234 cases of gastric ulcer examined post mortem, Boudreau and Harvey[13] decided that the oft-quoted clinical guides such as size and location of the ulcer give no clue to its true nature. The coexistence of a duodenal ulcer and a gastric ulcer is also no assurance that the latter is benign. In a report of 73 cases of gastric ulcer considered benign clinically and found to be malignant at operation Lampert, Waugh and Dockerty[7] noted that 16 had an associated duodenal ulcer. Gastroscopic examination, which had been done in 9 cases, had given misleading information in each. In a group of 44 patients with malignant ulcer who were operated on Smith and Jordan[4] reported that the original diagnosis was benign in half the cases. In 10, operation was delayed from six months to seven years, during which the patients received medical management in or outside the hospital. In 2 other cases all clinical and roentgenologic

signs of ulcer had disappeared after treatment, and the patients were operated on four to six months later because of recurrence. In 14 cases an associated x-ray finding of duodenal ulcer was reported. In the cases in which gastroscopic examination was performed the diagnosis was in error in 27 per cent and in another 25 per cent of the examinations the lesion was not visualized. These observers emphasized the point that the symptoms are disarmingly similar in the benign and the malignant cases, and at times are absent in the presence of an active lesion.

In retrospect only 1 of our 8 cases of malignant ulcer satisfied the currently accepted rigid radiologic criteria for complete healing of the lesion. In 5 cases the location of the ulcer in the region of the cardia and its relative inaccessibility to cure except by radical operation at a risk exceeding the probabilities of carcinoma must have influenced the decision to carry on with medical measures. One patient with a large ulcer in the cardia was treated in hospitals repeatedly during a sixteen-year period for recurrent pain and hematemeses. Early in the course of his disease the ulcer had been cauterized at operation. Repeated x-ray examinations throughout the ensuing years always disclosed an active ulcer in the cardia. Eventually, at a second operation thirteen years after the cauterization a carcinoma of the stomach was discovered. Another patient with a lesion in the pars media of the stomach was treated surgically by local cauterization and then followed medically. X-ray studies a year later were reported to show a normal stomach. The patient had a severe recurrence eight years later and died of carcinoma of the stomach eleven years after the original hospitalization. Smith and Jordan[4] report a case of gastric ulcer treated as benign and proved at post-mortem examination twenty-three years later to be malignant.

The course of these 8 patients after discharge from the hospital is especially significant in that 6 disappeared promptly from medical observation and did not return until compelled by a recurrence of symptoms. The practical difficulties in maintaining supervision over these cases were recognized by Grimes and Bell,[3] who found that only half their cases of malignant gastric ulcer had been properly checked by radiologic studies. In our group the average interval between initial hospitalization and death from carcinoma of the stomach was five years.

Two important questions in the management of the patient with gastric ulcer require an explicit answer. How long should an ostensibly favorable case be continued on a trial of medical management in the hospital before one decides on operation? When all subjective symptoms and objective signs are favorable, the patient may be treated for a maximum of eight weeks provided there is distinct and progressive evidence of healing on serial x-ray examinations. It must be recognized that some patients operated on because of failure to heal within this interval will prove to have a benign lesion, but such a policy affords greater protection to the patient than one of procrastination and unfounded optimism. The second question concerns the potentiality of the recurrent ulcer to become malignant. Is the recurrence of a gastric ulcer an indication for resection on this basis alone? The evidence available in the literature does not appear to support such a routine procedure. The hypothesis that the recurrent gastric ulcer is more prone to malignant change than the original ulcer remains to be proved. A clinical study showing a correlation between the incidence of malignant degeneration and the frequency of recurrences would be suggestive but not conclusive evidence. A policy of resection for any recurrence because of fear of malignancy implies that all patients with gastric ulcer should be operated on as soon as the original diagnosis is made. Since recurrences may be expected in 50 to 90 per cent of cases during a five-year follow-up period, it seems only logical to have the operation done promptly and thus to protect the patient from an almost inevitable double jeopardy of cancer. Unless one is prepared to adopt such a policy it is preferable to consider each recurrence on its merits and to reserve surgery for cases that have recurred under good medical management, fail to heal promptly or present the serious complications that often characterize the reactivation of a gastric ulcer. Also, surgical treatment is probably a wiser choice when the patient has demonstrated his unwillingness or inability to co-operate in a carefully administered medical regimen.

In view of the hazards involved, the conclusion is inescapable that the patient who is found to have a gastric ulcer must be admitted to the hospital at once for evaluation and decision concerning the method of therapy indicated. To treat a gastric ulcer on an ambulatory basis is to invite disaster. The *sine qua non* for the continuation of conservative medical treatment in the hospital is the progressive diminution in size of the gastric ulcer on serial radiologic examination, and the indispensable prerequisite for discharge of the patient is the complete disappearance of the lesion, with return of normal pliability of the gastric wall in that area. Subsequent medical management must include a regular semiannual radiologic examination of the stomach for three years and annually thereafter, regardless of the absence of digestive symptoms. To ensure the full co-operation of the patient in this program, one should inform him of the potentialities of his disease in clear and unmistakable terms: he must understand that his is a continuing problem, and that in accepting medical rather than surgical treatment he obligates himself to report at regular intervals for medical supervision and to return immediately for examination if symptoms

recur. The physician himself carries the special responsibility of maintaining contact with the patient throughout the ensuing years so that he is never lost from view.

Summary and Conclusions

The prognosis of gastric ulcer under medical treatment as reflected in the probability of present or future carcinoma and in the incidence of recurrences and complications is far from reassuring. Our experience suggests that when rigid clinical and laboratory safeguards are carefully employed the patient with an uncomplicated gastric ulcer may be treated medically at a risk of malignant degeneration that compares favorably with the operative mortality of resection. This survey indicates, however, that in actual practice these safeguards are often disregarded by physician and patient alike so that medical treatment can become a desultory and perilous form of therapy. Unless the immediate and future circumstances appear optimal in terms of patient amenability and responsibility, surgery may be the only direct and practical answer to the problem for most cases. There is need for wider publicity of the known facts concerning gastric ulcer among the profession and the public.

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References

1. Mallory, T. B. Carcinoma in situ of stomach and its bearing on histogenesis of malignant ulcer. *Arch. Path.* **30**:348-362, 1940.
2. Walters, W. Gastric ulcer: carcinomatous ulcer or ulcerating carcinoma? *Ann. Surg.* **115**:521-529, 1942.
3. Grimes, O. F., and Bell, H. G. Clinical and pathological studies of benign and malignant gastric ulcers. *Surg., Gynec. & Obst.* **90**: 359-371, 1950.
4. Smith, F. H., and Jordan, S. M. Gastric ulcer: study of 600 cases. *Gastroenterology* **11**:575-597, 1948.
5. Marshall, S. F., and Welch, M. L. Results of surgical treatment for gastric ulcer. *J. A. M. A.* **136**:748-752, 1948.
6. Lahey, F. H., and Marshall, S. F. Surgical treatment of peptic ulcer. *New Eng. J. Med.* **246**:115-123, 1952.
7. Lampert, E. G., Waugh, J. M., and Dockerty, M. B. Incidence of malignancy in gastric ulcers believed preoperatively to be benign. *Surg., Gynec. & Obst.* **91**:673-679, 1950.
8. Flood, C. A., and Hennig, G. C. Recurrence in gastric ulcer under medical management. *Gastroenterology* **16**:57-72, 1950.
9. Palmer, E. D. Clinical significance of small benign gastric ulcer, with note on benign ulcer of greater curvature and in absence of free hydrochloric acid. *Am. J. M. Sc.* **223**:386-391, 1952.
10. Welch, C. E., and Allen, A. W. Gastric ulcer: study of Massachusetts General Hospital cases during ten-year period, 1938-1947. *New Eng. J. Med.* **240**:277-283, 1949.
11. Judd, E. S., and Priestley, J. T. Treatment of gastric ulcer. *Surg., Gynec. & Obst.* **77**:21-25, 1943.
12. Allen, A. W., and Welch, C. E. Gastric ulcer: significance of this diagnosis and its relationship to cancer. *Ann. Surg.* **114**:498-509, 1941.
13. Boudreau, R. P., and Harvey, J. P., Jr. Anatomic study of benign and malignant gastric ulcerations. *J. A. M. A.* **147**:374-377, 1951.

A CASE OF PULMONARY TULAREMIA TREATED WITH AUREOMYCIN*

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TULAREMIA, an acute disease caused by infection with *Pasteurella tularensis*, is widespread among animals and not uncommon in man. The organisms are usually transmitted by the bites of blood-sucking insects, by handling of sick rabbits and, rarely, by the ingestion of insufficiently cooked meat of an infected animal. The period of incubation is two to five days. The onset is sudden, with chill, fever, headache and general aching. There may be a generalized rash.[1] Tularemia is usually divided into five types: ulceroglandular (the most common), oculoglandular, glandular, typhoidal and pulmonary. The diagnosis of pulmonary tularemia, sometimes difficult because of the nonspecificity of symptoms and signs,[2] is generally made by the specific agglutination test, which becomes positive in two weeks, and which may reach a titer as high as 1:1,280 during the third week. The agglutination titer remains high for years. Cultures may be obtained in the first week, but require a special medium, which is usually not available in a general hospital.

Until 1944 there was no effective specific treatment for tularemia. In that year, Heilman[3] reported that streptomycin was effective in experimental tularemia, and this remained the treatment of choice and the only effective therapy until 1949,[4] when Woodward et al.[5] and Ransmeier[6] reported their studies on the treatment of experimental and clinical tularemia with aureomycin. Chloramphenicol has been reported to be clinically effective against *Past. tularensis* but is not as satisfactory as streptomycin or aureomycin; experimental studies with this antibiotic have been disappointing.[7] In 1951, it was recommended that both streptomycin and aureomycin be used in the treatment of tularemia, and that a few days be allowed to elapse before treatment is started, so that an immunity may develop.[8] Several reports published before and since that time indicate that aureomycin may become the treament of choice in this disease.[5, 9-12]

The case reported below is thought to be especially interesting for several reasons: it is the first case of tularemia to be recorded in the hospitals of Orlando, Florida, since permanent records have been kept (eighteen years); according to the available literature, it is the second case of tularemia with probable pericarditis treated with aureomycin to be reported; the apparent method of

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transmission is a rather unusual one; and the case emphasizes the nonspecificity of symptoms and signs and the ease with which the diagnosis may be made if the possibility of tularemia is kept in mind.

Case Report

A 45-year-old man was admitted to the hospital in September, 1952. Four days previously a severe headache, pain in the back of the neck, and a temperature of 102°F. had suddenly developed. On the next day, because the symptoms persisted, he visited his physician, who treated him symptomatically for "flu." At that time, he began to exhibit slight disorientation. That night pleuritic pain in the left posterior and lateral portions of the chest developed. These symptoms continued, and the temperature rose to 104°F., remaining constantly at that level. Two days later he began to have a slightly productive cough and wheezing respirations. He was then given penicillin, 800,000 units daily for 2 days, without benefit.

Detailed questioning revealed no history of contact with animals, animal leavings or insect bites of any kind. Later, after the diagnosis was established, careful questioning brought out the fact that the patient had swept out the back of a pet-shop delivery truck about 4 days before the onset of his illness, while engaged as a service-station attendant. He stated that there were no animals in the truck at the time, and that as far as he knew, he had not received a flea bite or other insect bite.

Physical examination showed a man who appeared acutely and critically ill. The sensorium was cloudy. The mouth and pharynx were hyperemic. Fine moist rales were heard throughout the right-lung field. There was slight direct tenderness in the right upper part of the abdomen. Neurologic examination was negative except for clouding of the sensorium. Rectal examination was normal except for a slightly enlarged prostate, with some induration in the right lobe. The patient had had an involuntary watery bowel movement in the bed.

The temperature was 101°F., the pulse 105, and the respirations 25. The blood pressure was 114/78.

The diagnosis was atypical pneumonia.

The urine, which had a specific gravity of 1.005 and a pH of 4.5, gave a + test for albumin, and the sediment contained 15 white cells and 2 red cells per high-power field. Examination of the blood disclosed a red-cell count of 4,930,000, with a hemoglobin of 93 per cent, and a white-cell count of 6050, with 20 per cent stab and 76 per cent segmented neutrophils, 3 per cent lymphocytes and 1 per cent monocytes. Initial agglutinations against several organisms, including *Past. tularensis*, were negative. Stool examinations revealed the presence of a flagellate, *Enteromonas hominis*, and stool cultures grew an organism identified as a salmonella but not further identifiable.

Cold and heterophil-antibody agglutinations were negative at several examinations. An x-ray film of the chest showed a diffuse, fine infiltration throughout both lungs, more marked in the right upper lung, associated with infiltration extending out from both hili. No pleural reaction was seen. Routine sputum smears and cultures were not remarkable. The spinal fluid was normal. The blood urea nitrogen was 60 mg. per 100 cc. An electrocardiogram taken five days after admission revealed a low-voltage QRS complex, left-axis deviation, elevation of the ST segments in Leads 2, V_2, V_3, V_4, and V_5, and diphasic to flat T waves in all leads except V_1, where the waves were upright. The record was interpreted as not diagnostic, but probably representing an acute pericarditis. An electrocardiogram taken 2 days later demonstrated the same changes to a lesser degree and was interpreted as evidence of improvement. A posteroanterior x-ray film of the chest taken on the 7th hospital day showed some clearing of the infiltration in the lungs. Agglutination against *Past. tularensis* 16 days after the onset of illness was positive in a dilution of 1:320 (as high as the dilution was made); 24 days after the onset of illness agglutination was positive in dilutions up to 1:10,240.

On admission aureomycin, 500 mg. by vein, was begun and the patient was then given aureomycin by mouth, 500 mg. every 6 hours. The temperature rapidly rose to 104°F. and then fell to normal in the course of 24 hours, remaining so for the rest of the hospital stay, except for 1 elevation to 100.6°F. on the 3d day. The mental cloudiness diminished somewhat more slowly. The watery bowel movements continued for several days. On the 3d hospital day acute urinary retention developed, with an increase in the uremia, which responded well to conservative treatment. On the 5th hospital day (and 5th day of aureomycin treatment) an acute fairly severe stomatitis, which responded to nonspecific treatment without cessation of aureomycin administration, occurred. He was discharged after 12 days in the hospital, having been clinically well for several days.

Summary

A brief description of tularemia and the development of its treatment with antibiotics is given. There is evidence that aureomycin may become the treatment of choice in this disease.

A case of pulmonary tularemia with probable pericarditis successfully treated with aureomycin is presented. This is thought to be the second case of pulmonary tularemia with pericarditis treated with aureomycin to be reported in the medical literature.

As far as can be determined, this is the first hospitalized case of tularemia to be recorded in this section of Florida in the past eighteen years.

The suggestion is made that the disease was contracted from animal detritus with which the patient came in contact while cleaning out a pet-shop delivery truck. No other source of infection could be elicited.

Pulmonary tularemia presents some problems in early diagnosis because of the nonspecificity of symptoms and signs, as shown by this case. The possibility should be considered in severe atypical pneumonia.

References

1. Yater, W. M. *Fundamentals of Internal Medicine*. Third edition. 1451 pp. New York: Appleton-Century Crofts, Inc., 1949.
2. Crellin, J. A., Pugh, T. F., and Janton, O. H. Case of fatal tularemic pneumonia with necropsy. *Dis. of Chest* **16**:103-108, 1949.
3. Heilman, F. R. Streptomycin in treatment of experimental tularemia. *Proc. Staff. Meet., Mayo Clin.* **19**:553-559, 1944.
4. Foshay, L. Diagnosis and treatment of tularemia. *Postgrad. Med.* **4**:315-321, 1948.
5. Woodward, T. E., Raby, W. T., Eppes, W., Holbrook, W. A., and Hightower, J. A. Auromycin in treatment of experimental and human tularemia. *J. A. M. A.* **139**:830-832, 1949.
6. Ransmeier, J. C. Symposium on antibiotics: effect of aureomycin against *Bacterium tularense*. *J. Clin. Investigation* **28**:977-982, 1949.
7. Parker, R. T., Lister, L. M., Bauer, R. E., Hall, H. E., and Woodward, T. E. Use of chloramphenicol (chloromycetin) in experimental and human tularemia. *J. A. M. A.* **143**:7-11, 1950.
8. Adelson, S., Spalding, E. D., Thosteson, G., Watts, F., Jr, and Reveno, W. S. Highlights—1951 meeting American College of Physicians. *Harper Hosp. Bull.* **9**:86-101, 1951.
9. Long, P. H., Chandler, C. A., Bliss, E. A., Bryer, M. S., and Schoenbach, E. B. Use of antibiotics. *J. A. M. A.* **141**:315-317, 1949.
10. Lindeke, H. I., and Maiden, S. D. Oculoglandular tularemia treated with aureomycin. *J. A. M. A.* **142**:99, 1950.
11. Woodward, T. E. Chloromycetin and aureomycin: therapeutic results. *Ann. Int. Med.* **31**:53-82, 1949.
12. Corwin, W. C., and Stubbs, S. P. Further studies on tularemia in Ozarks. *J. A. M. A.* **149**:343, 1952.

MEDICAL PROGRESS

TREATMENT OF PEPTIC ULCER (Concluded)

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ACTH IN PEPTIC ULCER

The experiences with ACTH and cortisone in peptic ulcer provide an interesting commentary on the applicability to clinical medicine of results derived from animal experimentation. There were several considerations that suggested the importance of the pituitary-gonadal mechanism in the pathogenesis of peptic ulcer.[94] The relative infrequency of ulcers in women, the beneficial effect of pregnancy on ulcer symptoms and the frequent aggravation of these symptoms after the menopause, as well as the fact that the anterior pituitary gland undergoes hypertrophy during pregnancy, led to the theory that a protective substance against ulcer was elaborated by the pituitary hormones during the reproductive period. In view of the fact that Hench had noted a remission in rheumatoid arthritis with pregnancy and that ACTH was helpful in that disease, it was thought that ulcers, which were similarly improved with pregnancy, might also be amenable to treatment with the hormone. Experimentally, in Mann–Williamson dogs given ACTH and cortisone, the survival time was considerably longer than that in untreated animals.[94] However, when an attempt was made to transfer these results, based on theoretical and laboratory grounds, to patients, it soon became obvious that the preparations either aggravated the signs and symptoms of peptic ulcer or induced their appearance for the first time.[95-99]

As in other conditions in which the therapeutic effectiveness of ACTH and cortisone has been disappointing, their availability has provided a tool for elucidating hitherto obscure mechanisms in the pathogenesis of disease. ACTH and cortisone caused a pronounced increase in acid and pepsin secretion in the stomach and uropepsin excretion in the urine, that could be correlated with the initiation of symptoms in patients with peptic ulcer.[99] Although the vagus nerve remains the neurogenic pathway for mediating the effect of emotions from the hypothalamus to the stomach, it is now suggested on the basis of these studies that in response to chronic stress, the stomach may be influenced additionally through a humoral mechanism by way of the hypothalamic-pituitary-adrenal-gastric axis.[99, 100]

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EMOTIONS, PSYCHE AND ULCER

The classic work of Beaumont[101] and the later remarks of Cannon[102] on the effect of emotions on gastric physiology established the pattern for subsequent study relating psychogenic factors to dyspepsia.[103] This led to the current concept that peptic ulcer is a somatic representation of chronic dysfunction of the vegetative nervous system induced by stresses involving, in part, problems of interpersonal relations.[104, 105] That anxiety in association with conscious feelings of hostility and resentment may result in a state of gastric hyperfunction is strongly suggested by the studies of Wolf and Wolff[46] on their human subject, Tom. The hyperemia, hypersecretion and hypermotility reflecting this hyperfunction were associated in their test case with sufficient increase in mucosal vulnerability to favor the production of erosions and ulceration.

Margolin et al.,[106] however, in studying a female patient with a gastric fistula, suggested that the matter is more complex. Using a psychoanalytic technic, they considered the unconscious mental content the primary determinant in the physiologic changes observed. They noted, moreover, a dissociation of the physiologic phenomena of hypersecretion, hypermotility, and hyperemia rather than a constant association of these findings as in Tom. Thus, the total psychologic situation, including the unconscious, must be considered in attempts to correlate mental content and behavior with physiologic responses in the human stomach.

The attempt to construct a specific personality profile or conflict situation for the patient with ulcer is perhaps an unwarranted extension of Alexander's[104] views, as pointed out by Stine and Ivy[107] in their effort to determine the merits of psychoanalytic therapy in this disease. Alexander originally described 6 patients with duodenal ulcer and 3 with a gastric neurosis in whom he found evidence of a conflict developing from an unconscious longing to remain in an infantile, dependent relation on the one hand and a reactive striving of the adult for independence and self-sufficiency on the other. This frustration may then lead to a regression to levels where a wish to be fed is equated with that of being loved and dependent. The interpretation was made that constant stimulation of the stomach produces a state of gastric dysfunction independent of the normal food hunger stimulus and that ulcer

symptoms result when these wishes to be cared for by others are frustrated by an environment that does not permit their gratification in normal life relations. The major thesis in this concept is that "disturbance of function of an organ if persistent may lead to structural tissue changes."[104] The patient with ulcer, in his overt behavior as a reaction to his basic dependency, may show an exaggerated degree of aggressive independence, burdening himself with excessive responsibility and being reluctant to seek help from others. Admission to a hospital or submission to the active care of a physician gains therapeutic value for the patient by removing him from his responsibilities and conflict. Society sanctions such a capitulation to his inner dependency needs in the face of severe organic signs and symptoms such as the tangible evidence of a hemorrhage, vomiting or severe pain.

Though many studies,[108, 109] embracing approximately three hundred cases, in the psychiatric literature tend to confirm the presence of such a conflict situation, others[110] find a diversity of psychologic situations. There are no reports on the incidence of this specific type of conflict among the nonulcer population.[111] This information is essential before specific psychodynamic features can be related to psychosomatic disorders. Alexander was careful to point out that the conflict situation was not to be considered the sole factor, nor did he believe that it inevitably led to ulcer.

An interesting explanation of the decreasing incidence of ulcers in women is offered in the light of Alexander's work. With a change in the cultural pattern of modern life from Victorian restrictions to the freedom of their newly won social status, women are able to express emotional tension in a manner consistent with normal life situations.

Eighty per cent of analysts answering a questionnaire said that they had had no experience with ulcer patients in analysis.[107] This may have been due either to the resistance of ulcer patients to accepting such treatment[112] or to the fact that the neurotic behavior of patients who consult a psychoanalyst offered sufficient relief of the emotional tension to preclude the vegetative-nervous-system dysfunction as a possible precursor of peptic ulcer.[107] Of 7 patients with peptic ulcer who had been psychoanalyzed and whose records were deemed suitable for study, only 2 had remained free of the disease though 3 others were improved. Further reports of the value of this therapeutic approach will be awaited with interest without necessarily involving a judgment on the etiologic influence of emotional disturbances in peptic ulcer.

The beneficial effect of a regimen that may have furnished nothing more than a favorable environment[113, 114] as a form of simple superficial psychotherapy is suggested by a study of patients with ulcer in a Veterans Administration hospital.[115] The control group was given the usual medical treatment of bland diet, frequent feedings and antacid medication. The test group had no restrictions on diet or smoking and were seen in discussion sessions, where the relation between emotional tension, pain and ulcer was demonstrated. In addition, individual interviews with the ward physician, occupational therapy and guidance by a social worker were provided. There was no evidence that the patients who were not given a bland diet and antacid medication suffered from this deprivation. In fact, they became symptom free and ready for discharge in eighteen days, in contrast to the twenty-four days required for the control group. Such a result makes one pause before attributing therapeutic significance to any drug or diet.

X-Ray Therapy

X-rays directed to the fundus and body of the stomach have an effect on gastric secretion that, though unpredictable in its extent, depends in general on the intensity of the radiation applied.[116] Histologically, the changes observed in the stomach vary from an acute transitory inflammation to permanent atrophy. Anacidity has been observed to follow appropriate dosage (1100 to 2500 r) in approximately two thirds of the gastric ulcers and one third of the duodenal ulcers.[117, 118] This maximum effect is usually obtainable in thirty days and varies in duration from a few days to at least eight years. Healing of the ulcer can be correlated especially with the achlorhydria produced in that the ulcer has been observed to heal in all cases of anacidity, and no recurrence has been noted when this degree of inhibition of acid formation has been retained. Though no untoward effects are noted clinically in these patients with achlorhydria and atrophy of the gastric mucosa, it is the possibility of harmful sequelae to this atrophy as well as the variable and unpredictable result that has limited the use of this form of therapy to persons who are poor surgical risks, or have persistence of ulcer activity and free hydrochloric acid even after extensive operations.

The use of radium needles introduced through a stomach tube and in contact with gastric mucosa has produced some mucosal reaction, with reduction in acidity and symptomatic relief without evidence of damage to neighboring structures.[119] The possibility of distending a balloon at the end of a stomach tube with radioactive material in contact with gastric mucosa is another promising development in this general field of inhibiting gastric secretion.

Hemorrhage

"Published statistics are the basis of all unsound teaching, since they never present average results, only those so much better than average that they induce the doctor to collect them." This cynicism was expressed by Ogilvie[31] in connection with the results of treatment of peptic ulcer in general, but

the statement is especially pertinent as a preface to a discussion of the most common complication of ulcer—hemorrhage. Collected series fail to distinguish between their varying sources — whether drawn from private or clinic patients or municipal or private hospitals.[120] The compilation of many series, each consisting of a small number of cases, tends to exaggerate the erroneous conclusions derived from such samplings. The diagnostic criteria of the severity of the hemorrhage are either not recorded or lacking in conformity so that it is difficult to compare results obtained with various types of therapy. As Welch[121] has shown in his own series, by raising the upper limit of definition for massive hemorrhage from a red-cell count of 2,500,000 to one of 3,000,000, the mortality figures could be changed from 13 to 8 per cent. One must first look to this lack of statistical homogeneity for an explanation of the reported discrepancy in mortality figures before evaluating the significance that should be attributed to the content of the therapy used in any individual series.

A survey of the recent literature[122] focuses attention on the importance of several principles applied to the treatment of this complication. Since Meulengracht[123] emphasized his "free-feeding program" of frequent administration of adequate amounts of bland food as tolerated, the beneficial effects of this regimen have been generally established.[124] In contrast to the older method of immobilization and starvation during the period of bleeding, with mortality rates of 8 to 10 per cent, it has greatly simplified the care of the patient and has been associated in general with lower mortality rates averaging 2.5 per cent in series comparable in all respects except the type of management.[125] Although some modifications have been introduced, varying from no oral feeding for the first twenty-four hours to a gradual progression through various stages of a Sippy diet, the tendency has been toward a more liberal program of prompt, frequent and adequate feedings,[124] with the use of barbiturates for sedation and frequent injections of vitamins C and K, especially when the diet has previously been suboptimal. The objections to the use of morphine to allay anxiety are based on the frequency of nausea and vomiting; its effect in diminishing the tone of the upper gastrointestinal tract may interfere with retraction and healing.[124]

Another factor has been the recognition of the vital importance of blood replacement either as an adjunct to conservative measures or in preparation for surgery.[126, 127] The objections to transfusion,[120] however, have not completely died down and include the following: blood infusions, by raising the blood pressure, may increase or induce fresh bleeding; pyrexic reactions with associated chills may aggravate an already serious situation; transfusions may overload the circulation and result in pulmonary edema; and frequent transfusions may lead to serum hepatitis or Rh sensitization in young women. Most of these arguments have been taken into consideration in present-day management of severe bleeding by blood replacement, with the decision usually rendered in favor of transfusions with discretion.[128] Blood running into a vein by the drip method at a rate of 40 to 50 drops a minute produces no significant rise in blood pressure. Although it is perhaps true that for the first few hours after a brisk hemorrhage the decrease in blood volume operates in favor of cessation of bleeding, this advantage is soon lost by the corrective influence of spontaneous hemodilution. When the systolic blood pressure drops below 90 with a rising pulse, or the hemoglobin determination, hematocrit or blood-volume studies show more than 50 per cent exsanguination, adequate blood replacement will counteract shock, lessen the danger of anoxemia and protect the heart from the increased burden of anemia. If bleeding recurs or operation becomes necessary such a program will help to transform a desperate situation into a tolerable one.

Many clinicians are so favorably impressed with the results of conservative treatment of feeding and blood replacement, as outlined above, that they will accept a certain irreducible mortality rather than agree to any therapeutic role for the surgeon unless the bleeding is complicated by perforation.[124]

The other extreme of this picture is presented by those who consider the best treatment for severe bleeding of peptic ulcer to be surgical, since it represents a serious complication with a grave prognosis if uncorrected.[129, 130] The difficulty in predicting the outcome in the individual case makes them believe that definitive surgery should be undertaken when there is reasonably good evidence for the diagnosis of peptic ulcer and when there is a loss of more than 40 per cent of the circulating blood from hemorrhage within a week of hospitalization. Stewart et al.[129] have been the leading proponents of such surgical measures and have recorded a surgical mortality of 11 per cent during a five-year experience with 110 patients — the average patient being subjected to operation after and during blood replacement within seven and a half hours of admission.

The crux of the problem lies in one's inability to choose, from among the patients with severe hemorrhage, those who will not survive unless a surgical attempt is made to arrest the bleeding.[131] Criteria have been set up in an effort to distinguish between these two groups more accurately,[132] with the active co-operation of teams consisting of an internist ("keen and young"), a surgeon ("somewhat reluctant"),[133] a roentgenologist trained in the technic of examining the upper gastrointestinal tract soon after bleeding according to the Hampton procedure[134, 135] and a skilled anesthetist to deal with patients whose condition may be bordering on shock. Although certain generalizations are per-

missible as a result of such studies with this combined method of management, they can serve only as guides and not as hard-and-fast rules in any individual case. One can in general but not specifically predict a more serious situation and advise surgical intervention before the patient's general condition deteriorates under the following circumstances: persistent bleeding with hematemesis for more than forty-eight hours, with failure to obtain stabilization after 1.5 to 2 liters of blood; the recurrence of bleeding under hospital management; and the presence of associated complicating conditions such as age over fifty, arteriosclerosis, hypertension, heart disease and cirrhosis of the liver with portal hypertension.[128, 132] Whereas the young patient seldom dies of a hemorrhage, such an assurance is not to be taken as a guarantee of immunity, since many series[121] report deaths in patients below the age of forty, whether they are treated conservatively or surgically.

The possibility of early emergency operation enhances the importance of accuracy in diagnosis. The value of the bromsulfalein test for screening purposes in cirrhosis of the liver has recently been emphasized,[136] the level of 15 per cent retention in the blood after forty-five minutes being considered suspicious for cirrhosis and possible varices. Such a diagnosis by no means precludes the additional one of ulcer in view of the frequent association of the two. Early x-ray investigation to establish the diagnosis of ulcer is indicated in cases without a previous diagnosis or adequate history, in which the question of surgical intervention depends primarily on the confirmation of an ulcer.[131] The objections to this early x-ray examination — that it may induce bleeding, or that the presence of blood clots may lead to confusion and misinterpretation — are calculated risks that may in part be minimized by the skill and experience of the roentgenologist but, in any case, must be weighed against the danger of treating the patients without a definite diagnosis.[137, 138]

Such policies will undoubtedly bring to surgery many patients who would have stopped bleeding if maintained on a conservative regimen, but they derive their support from the assumption that they will ensure the inclusion of all patients whose bleeding is remediable only by surgical intervention.[131] The mortality in such combined methods of treatment has recently varied from 1.3 to 8 per cent,[121, 131] as contrasted with Miller's[124] figure of 2.5 per cent when medical treatment alone was used in all cases and Stewart's[120] figures of 11 per cent when all patients were subjected to operation on the basis of the criteria outlined above.

From a consideration of these factors, one may anticipate the best results in this serious complication from the combined efforts of internists and surgeons in assessing the condition, diagnosis and treatment of the individual patient. The case for surgery alone, as the foremost plan of treatment, though attended in certain hands with admirable statistical results, will not compare favorably with either of the two more conservative regimens.

Although the mortality is apparently greatest with the first hemorrhage,[128] the incidence of recurrent bleeding is sufficiently high (70 to 85 per cent) to warrant consideration of a definitive operation in the interval, especially if previous medical care has been adequate and the patient has had at least one previous hemorrhage.

Perforation

The recent publication[139-152] of several reports on the conservative treatment of perforation was suggested in part by the frequent finding on exploration that the perforation was already sealed off and the peritoneal contents sterile, especially in early cases. This nonsurgical treatment of perforation consists of constant gastric suction with nothing by mouth for at least twenty-four hours, fluid requirements being maintained intravenously and peritonitis combated with antibiotics. The subsequent therapy depends on the clinical course, the degree of gastric retention and the signs of peritoneal irritation. It would be most unfortunate if these reports were to lead to the universal adoption of such nonsurgical measures unless adequate surgical facilities are unobtainable, or the patient's general condition is so poor as to make the risk of surgery prohibitive. When this method has been adopted as the treatment of choice, the hazards of faulty diagnosis or persistent leakage from swallowed air that keeps the perforation from closing have led to grave consequences unless recognized early and correctly dealt with.[142] There are two other conditions in which conservative therapy may be considered, especially if proper surgical facilities are not available: a *forme fruste* perforation, with rapid sealing off and localization of the peritonitis, and the sterile perforation as an accident of gastroscopy. The recent marked reduction in the operative mortality (from 20 to 2 per cent) attributable to improvements in diagnosis, chemotherapy and fluid-balance management, makes surgical repair preferable to any other form of treatment under ordinary conditions.[144]

Obstruction

Although interference with the passage of food from the stomach through the duodenum is a common complication of peptic ulcer, this is usually due to spasm and edema and responds favorably to the conventional measures for treatment of the active ulcer. Even more prolonged obstruction, in which the element of scarring in or about the pylorus and duodenal cap is the most important feature, may show a temporary improvement depending on how much functional obstruction from spasm and edema contributes to the retention.

Various methods have been used to differentiate these two mechanisms and their relative role in any individual case. Some prefer to omit all feeding by mouth for at least twenty-four to forty-eight hours, during which constant or intermittent aspiration is undertaken and fluid and electrolyte balance is maintained parenterally. Milk and other antacids may then be fed in small amounts at frequent and regular intervals, usually hourly, with intermittent aspiration starting thirty minutes after each feeding and continuing to the next period, to permit beneficial effect of neutralization on the active ulcer and yet to protect the obstructed stomach from overdistention.[145] Any obstruction that fails to respond to this treatment after it has been in operation for more than three days should be considered a surgical problem. Whereas it is true that more prolonged treatment may result eventually in further improvement, from a practical point of view this delay indicates a significant amount of organic obstruction that can only lead to further difficulties in the future. This method not only helps one to make a definitive diagnosis of the nature and degree of the obstructing process but also prepares the patient for operation by deflating the stomach and giving it a chance to regain its tone.

Intractability

Of the several complications of peptic ulcer for which surgery may be considered, intractability is the one most difficult to define, and yet it is necessary to do so precisely if proper therapy is to be instituted.[11, 20, 31] Specific knowledge must be obtained regarding the type of patient, the nature of his lesion and its complications, and the details of the treatment prescribed and followed, since the choice of eventual management will depend on these considerations.[146, 147]

The lesion may be so anatomically involved in surrounding tissues as a result of deep penetration or walled-off perforation that no conservative approach can ever induce healing and restore physiologic normality.[11, 80, 148] The patient's emotional life and milieu may be so disturbing or his reaction to it so profound as to call forth the utmost of the physician's "patience, perseverance, and skill"[149] to manipulate the environment or modify the patient's response to it. Careful review of the therapy may reveal that both the ulcer and the patient are quite tractable but that the regimen as outlined by the physician is inadequate to bring about control of the gastric acidity.[149]

Thus, before the interpretation of intractability can be justified, these factors must be considered if unnecessary operation and the high incidence of postoperative morbidity often seen in such cases are to be avoided.

Gastric Ulcer

Gastric ulcer is considered under a separate heading[150] rather than as a subdivision of peptic ulcer, to emphasize the special problem it presents in relation to gastric cancer. Although benign ulcers occurring on either side of the pylorus are peptic in origin, the element of hypersecretion with abnormally high acid values characterizes the duodenal ulcer, and the values below normal frequently seen in gastric ulcer place greater emphasis on increased mucosal vulnerability as the mechanism of ulceration. The treatment of the acute phase of activity, the response to such treatment and the tendency to recur are similar in both types of ulcer.[28, 29, 151] Ogilvie[31] has summarized certain differences between the two by suggesting that the cause of persistence of the gastric ulcer is to be found in the stomach itself, whereas the duodenal ulcer is a local manifestation of a general disease.

Much attention has been directed in the past to two phases of the gastric-ulcer problem — that is, the potentiality of malignant degeneration in a recurring benign ulcer, and the ability to differentiate the two so as to detect the presence of cancer in an ulcerating lesion.

The evidence in favor of malignant degeneration of a previously benign lesion is derived from both theoretical and pathological sources.[152] The analogy with chronic endocervicitis and ulcerative colitis suggests that chronic irritation, with frequent breaking down and repair of tissue, may set in motion cellular changes that lead to cancer. The finding of small foci of malignant cells at the edge of a chronic peptic ulcer in patients who have been followed for years, with frequent episodes of apparently benign ulcer activity, has been used to confirm this potentiality for malignant degeneration in some cases with gastric ulcer.

However, "analogy does not constitute proof."[153] Moreover, the concept of carcinoma in situ in addition to peptic ulceration provides an adequate explanation for the pathological association of carcinoma and ulceration.[154] Neoplastic foci may remain localized in a limited area of mucosa without invading other tissues and then undergo peptic ulceration in the presence of free hydrochloric acid. The ulceration thus produced may dominate the clinical picture, resembling in all ways the course of a benign peptic ulcer until the original malignant process becomes invasive. Thus, the smaller size of the neoplasm is no more an index of recent origin than the degree of scar formation in the base of the ulcer is a sign of its precedence.[153]

A more immediate and practical problem concerns the ability of the clinician to distinguish between benign and malignant ulcers of the stomach, utilizing all aids short of a histologic examination of the resected specimen.[153] It is on this point that the major divisions in therapy are focused. Statistics[155-157] have been quoted, some from the past before such refinements in technic as gastroscopy, mucosal relief x-ray studies and Papanicolaou staining of gastric aspirations were fully developed,

purporting to show a diagnostic error of 10 to 20 per cent. Many of these reports include without justification as errors in diagnosis patients who were carefully followed during a screening period of four to six weeks according to a prearranged plan before they were subjected to operation.

The arguments[145, 155-158] in favor of immediate operation for all gastric ulcers may be summarized as follows: there has been little improvement in the survival rate of patients with carcinoma of the stomach, in large part attributable to failure to make the diagnosis and obtain surgical care before metastases have occurred; radical resection in all cases with gastric ulcer before the diagnosis of cancer becomes obvious may salvage an appreciable number of early cases even though many patients thus treated will be proved to have a benign ulcer; one cannot make the distinction between benign and malignant ulcers with sufficient accuracy to permit conservative treatment and continued observation; the results of gastric resection are uniformly good, the mortality and incidence of recurrent ulceration being low; and to delay until the results of medical therapy are unequivocal may be hazardous so far as the optimum time for resectability is concerned.

The case against immediate surgical intervention rests on several considerations.[145, 152, 153, 158] The patient with a gastric ulcer, if he is to be treated conservatively, must be educated to the proposition that such a program represents a continuing problem for both patient and physician.[24] Although "there are no signs pathognomonic of benignancy,"[153] and there is no group of diagnostic measures that will ensure the permanent correctness of this approach,[159] it remains tenable if repeated observations continue to satisfy the following criteria: complete remission of all ulcer signs and symptoms such as pain, weight loss and melena, and the disappearance of all evidence of ulceration and rigidity of the wall as determined by x-ray and gastroscopic examination within four to six weeks under an optimum regimen. With the five-year cure for carcinoma of the stomach so poor and the average patient not being operated on for one and a half years after the onset of symptoms, a delay of four to six weeks under careful observation should not appreciably affect the ultimate results. However, the finding of persistent achlorhydria after histamine, a positive Papanicolaou test on gastric washings, a meniscus sign on x-ray examination, an ulcer on the greater curvature of the stomach and failure to satisfy all the criteria mentioned above call for immediate operation. When these principles of therapy are adhered to, the diagnostic error will compare favorably with the mortality (3 to 5 per cent) of gastric resection for benign ulcer.[150, 152] Furthermore, the excellent mortality figures reported from leading surgical clinics are not representative of the surgical statistics that will obtain in the country as a whole where the mass of surgery will be done. Nor can the morbidity entailed in such a surgical procedure with the resulting disturbances in gastric physiology be entirely ignored.

A review of post-mortem material,[160] which suffers from the exclusion of surgically resected specimens, indicates the unreliability of the patient's age or the size and location of the lesion in the differentiation of benign from malignant ulcers of the stomach. Approximately two thirds of the prepyloric ulcers were benign, as were half of 47 ulcers on the greater curvature. Of 25 patients with gastric ulcer over the age of eighty, the ulcers were benign in 18. Only half the malignant ulcers and as many as a tenth of the benign ulcers were larger than 4 cm. in diameter. Thus, none of these criteria are of individual pathognomonic diagnostic value except in combination with all the other pertinent clinical features.

Although the presence of duodenal ulcer has in the past[150, 160] cast an aura of benignancy on the gastric ulcer found in association with it, Smith and Jordan[152] found an x-ray defect in the duodenum in 31 per cent of proved malignant gastric ulcers.

Summary

Recent progress in the medical treatment of peptic ulcer is briefly reviewed. The role of diet, drugs, psychotherapy and radiation in the management of this disease is assessed in the light of conventional theories and newer contributions. The merits of medical and surgical treatment for the sequelae of ulcer are appraised, with especial attention to hemorrhage as the major complication. The question of malignant degeneration in a recurring benign ulcer and the difficulty in differentiating the two have led to a consideration of gastric ulcer as a separate topic.

References

94. Sandweiss, D. J., Saltzstein, H. C., Scheinberg, S. R., and Parks, A. Hormone studies in peptic ulcer: pituitary adrenocorticotropic hormone (ACTH) and cortisone. *J. A. M. A.* **144**:1436-1442, 1950.

95. Beck, J. C., Browne, J. S. L., Johnson, L. G., Kennedy, B. J., and MacKenzie, D. W. Occurrence of peritonitis during ACTH administration. *Canad. M. A. J.* **62**:423, 1950.

96. Habif, D. V., Hare, C. C., and Glaser, G. H. Perforated duodenal ulcer associated with (ACTH) therapy. *J. A. M. A.* **144**:996, 1950.

97. Smyth, G. A. Activation of peptic ulcer during pituitary adrenocorticotropic hormone treatment: report of three cases. *J. A. M. A.* **145**:474-477, 1951.

98. Kirsner, J. B., Klotz, A. P., and Palmer, W. L. Unfavorable course of gastric ulcer during administration of ACTH and cortisone. *Gastroenterology* **20**:27-29, 1952.

99. Gray, S. J., Benson, J. A., Jr., Reifenstein, R. W., and Spiro, H. M. Chronic stress and peptic ulcer. I. Effect of corticotropin (ACTH) and cortisone on gastric secretion. *J. A. M. A.* **147**:1529-1537, 1951.

100. Editorial. Hormones in peptic ulceration. *Lancet* **1**:201, 1952.

101. Beaumont, W. *Experiments and Observations on the Gastric Juice and the Physiology of Digestion.* 279 pp. Plattsburgh, New York: Allen Company, 1833.

102. Cannon, W. B. *Bodily Changes in Pain, Hunger, Fear, and Rage.* 311 pp. New York: Appleton, 1915.

103. Mittleman, B., and Wolf, H. G. Emotions and gastroduodenal function: experimental studies on patients with gastritis, duodenitis and peptic ulcer. *Psychosom. Med.* **4**:5-61, 1942.

104. Alexander, F. Influence of psychologic factors upon gastrointestinal disturbances: symposium: general principles, objectives and preliminary results. *Psychoanalyt. Quart.* **3**:501-539, 1934.

105. Wolf, S. Summary of evidence relating life situations and emotional response to peptic ulcer. *Ann. Int. Med.* **31**:637-649, 1949.
106. Margolin, S. G., et al. Variations of gastric functions during conscious and unconscious conflict states. *Proc. A. Res. Nerv. & Ment. Dis.* **29**:656-664, 1950.
107. Stine, L. A., and Ivy, A. C. Effect of psychoanalysis on course of peptic ulcer: preliminary report. *Gastroenterology* **21**:185-211, 1952.
108. Kezur, E., Kapp, F. T., and Rosenbaum, M. Psychological factors in women with peptic ulcers. *Am. J. Psychiat.* **108**:368-373, 1951.
109. Zane, M. D. Psychosomatic considerations in peptic ulcer. *Psychosom. Med.* **9**:372-380, 1947.
110. Cobb, S. In discussion of Ivy, A. C. Evidence pertaining to psychosomatic aspects of peptic ulcer. *J. Nerv. & Ment. Dis.* **111**:518-524, 1950.
111. Kahn, E., and Freyhan, F. A. Peptic ulcer — facts and assumptions. *Am. J. Psychiat.* **107**:866, 1951.
112. Sullivan, A. J., and McKell, T. E. *Personality in Peptic Ulcer.* 100 pp. Springfield, Illinois: Charles C Thomas, 1950.
113. Zetzel, L. Experiences with peptic ulcer in army station hospital. *Gastroenterology* **3**:472-479, 1944.
114. Gill, A. M. Pain and healing of peptic ulcer. *Lancet* **1**:291, 1947.
115. Selesnick, S. Psychotherapy in chronic peptic ulcer. *Gastroenterology* **14**:364-368, 1950.
116. Ricketts, W. E., Kirsner, J. B., Humphreys, E. M., and Palmer, W. L. Effect of roentgen irradiation on gastric mucosa. *Gastroenterology* **11**:818-832, 1949.
117. Ricketts, W. E., Palmer, W. L., Kirsner, J. B., and Hamann, A. Radiation therapy in peptic ulcer: analysis of results. *Gastroenterology* **11**:789-806, 1949.
118. *Idem.* Radiation therapy in peptic ulcer: study of selected cases. *Gastroenterology* **11**:807-817, 1949.
119. McGeorge, M. Results of treatment of gastric hyperacidity by radium, with special reference to duodenal ulceration. *Quart. J. Med.* **19**:111-128, 1950.
120. Jones, F. A. Haematemesis and melaena: with special reference to bleeding peptic ulcer. *Brit. M. J.* **2**:441-446, and 477-482, 1947.
121. Welch, C. E. Treatment of acute massive gastroduodenal hemorrhage. *J. A. M. A.* **141**:1113-1119, 1949.
122. Crohn, B. B., and Janowitz, H. D. Modern treatment of massive hemorrhage of peptic ulcer origin. *Gastroenterology* **19**:605-619, 1951.
123. Meulengracht, E. Treatment of hematemesis and melena without restriction of diet. *Ugesk. f. laeger* **95**:1257-1259, 1933.
124. Miller, T. G. Results from management of bleeding gastric and duodenal ulcer. *Ann. Int. Med.* **15**:390-394, 1941.
125. Meulengracht, E. Fifteen years' experience with free feeding of patients with bleeding peptic ulcer. *Arch. Int. Med.* **80**:697-708, 1947.
126. Lipp, W. F., Lipsitz, M. H., Milch, E., and Aaron, A. H. Management of massive hemorrhage from gastroduodenal ulceration. *J. A. M. A.* **145**:14-16, 1951.
127. Allen, A. W., and Welch, C. E. Abdominal surgery. *New Eng. J. Med.* **243**:16-23, 1950.
128. Pollard, H. M., and Wollum, A. Role of transfusions in management of gastric hemorrhage. *J. A. M. A.* **145**:22-24, 1951.
129. Stewart, J. D., Sanderson, G. M., and Wiles, C. E., Jr. Blood replacement and gastric resection for massively bleeding peptic ulcer. *Ann. Surg.* **136**:742-751, 1952.
130. Glenn, F., and Harrison, C. S. Surgical management of massive hemorrhage from peptic ulcer. *Arch. Surg.* **63**:766-773, 1951.
131. Warthin, T. A., Warren, R., and Wissing, E. G. Combined medical and surgical management of upper gastrointestinal hemorrhage. *New Eng. J. Med.* **241**:473-478, 1949.
132. Gray, S. J. Management of patients with massive hemorrhage from peptic ulcer. *M. Clin. North America* **31**:1121-1134, 1947.
133. Lewis, I. Discussion: gastroduodenal hemorrhage as surgical emergency. *Proc. Roy. Soc. Med.* **43**:145-156, 1950.
134. Hampton, A. O. Safe methods for roentgen demonstration of bleeding duodenal ulcers. *Am. J. Roentgenol.* **38**:565-570, 1937.
135. Schatzki, R. Roentgenologic examination in patients with bleeding from gastrointestinal tract. *New Eng. J. Med.* **235**:783-786, 1946.
136. Zamcheck, N., Chalmers, T. C., Ritvo, M., and Osborne, M. P. Early diagnosis in massive gastrointestinal hemorrhage. *J. A. M. A.* **148**:504-507, 1952.
137. Zamcheck, N., et al. Early roentgen diagnosis in massive bleeding from upper gastrointestinal tract: clinical evaluation of safety and reliability of method in 123 patients. *Am. J. Med.* **13**:713-724, 1952.
138. Jones, C. M. Symposium on gastrointestinal bleeding: diagnostic and therapeutic considerations of gastrointestinal bleeding. *New Eng. J. Med.* **235**:773-776, 1946.
139. Bedford-Turner, E. W. Conservative treatment of duodenal ulcer. *Brit. M. J.* **1**:457, 1945.
140. Taylor, H. Perforated peptic ulcer treated without operation. *Lancet* **2**:441-444, 1946.
141. Seeley, S. F., Hogan, E., Henry, J. R., and Bertram, H. F. Non-operative treatment of perforated peptic ulcer. *Bull. U. S. Army M. Dept.* **9**:124-130, 1949.
142. Chamberlain, D., Taylor, H., Doll, R., Bentley, J. F. R., and Lewis, I. Discussion on operative and conservative treatment of perforated peptic ulceration. *Proc. Roy. Soc. Med.* **44**:273-282, 1951.
143. Mikal, S., and Morrison, W. R. Acute perforated peptic ulcer: criteria for operation and analysis of 500 cases. *New Eng. J. Med.* **247**:119-123, 1952.
144. Vaughan, R. H., and Warren, R. Perforated peptic ulcer: study of indications for nonsurgical treatment in selected cases. *New Eng. J. Med.* **244**:898-902, 1951.
145. Wilkinson, S. A. Present status of peptic ulcer problem. *J. A. M. A.* **138**:805-807, 1948.
146. Palmer, W. L. Intractability in peptic ulcer. *Am. J. Med.* **5**:479-481, 1948.
147. Althausen, T. L. Prevention of recurrences in peptic ulcer. *Ann. Int. Med.* **30**:544-559, 1949.
148. Marion, D. F. Failures in medical treatment of peptic ulcer: analysis of intractability as indication for surgery. *South. M. J.* **44**:148-153, 1951.
149. Palmer, W. L., Kirsner, J. B., and Levin, I. Treatment of intractable peptic ulcer. *Ann. Int. Med.* **33**:590-601, 1950.
150. Welch, C. E., and Allen, A. W. Gastric ulcer: study of Massachusetts General Hospital cases during ten-year period, 1938-1947. *New Eng. J. Med.* **240**:277-283, 1949.
151. Bralow, S. P., Spellberg, M., Kroll, H., and Necheles, H. Peptic ulcer in man: evaluation of ulcer therapy. *Am. J. Digest. Dis. & Nutrition* **17**:119-124, 1950.
152. Smith, F. H., and Jordan, S. M. Gastric ulcer. Study of 600 cases. *Gastroenterology* **11**:575-597, 1948.
153. Palmer, W. L. Certain aspects of benign and malignant gastric ulcer. *Bull. New York Acad. Med.* **26**:527-537, 1950.
154. Mallory, T. B. Carcinoma in situ of stomach and its bearing on histogenesis of malignant ulcers. *Arch. Path.* **30**:348-362, 1940.
155. Lahey, F. H., and Marshall, S. F. Surgical treatment of peptic ulcer. *New Eng. J. Med.* **246**:115-123, 1952.
156. Marshall, S. F., and Welch, M. L. Results of surgical treatment for gastric ulcer. *J. A. M. A.* **136**:748-752, 1948.
157. Ransom, H. K. Subtotal gastrectomy for gastric ulcer: study of end results. *Ann. Surg.* **146**:633-654, 1947.
158. Bachrach, W. H. Management of gastric ulcer. *Ann. West. Med. & Surg.* **6**:145-153, 1952.
159. Banks, B. M., and Zetzel, L. Prognosis in gastric ulcer treated conservatively. *New Eng. J. Med.* **248**:1008-1013, 1953.
160. Boudreau, R. P., Harvey, J. P., Jr., and Robbins, S. L. Anatomic study of benign and malignant gastric ulcerations. *J. A. M. A.* **147**:374-377, 1951.
161. Fischer, A., Clagett, O. T., and McDonald, J. R. Coexistent duodenal ulcer and gastric malignancy. *Surgery* **21**:168-174, 1947.

MEDICAL INTELLIGENCE

ANAPHYLACTOID REACTION TO THE HYDRIODIDE OF DIETHYLAMINOETHYL ESTER OF PENICILLIN G (NEO-PENIL)

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THE hydriodide of diethylaminoethyl ester of penicillin G (Neo-Penil†) was released for general use early in the summer of 1952, after clinical investigation[1-3] had shown it to be safe and efficacious. In July, 1952, it was administered to a patient with advanced silicosis because of its reportedly selective concentration in inflamed pulmonary tissues.[4] After the third intramuscular injection in the usual doses of 500,000 units per cubic centimeter, the patient experienced an alarming anaphylactoid reaction from which he fortunately recovered. A report of a similar case has appeared in the English literature,[5] but to my knowledge no other case has been reported to date. In view of the more widespread use of Neo-Penil, this experience is reported in full.

CASE REPORT

J. P., a 69-year-old unemployed foundry worker, with known silicosis of 10 years' duration, has been attended by me for the past 6 years, during which his disease, characterized by dyspnea and recurrent pulmonic infections, had become gradually but progressively worse. On many occasions during this period, he was given procaine penicillin G in aqueous suspension for episodes of complicating pulmonary infection associated with retention of thick, bronchial secretions. Expectoration of less viscid sputum and defervescence of fever usually occurred promptly. None of the well known toxic reactions of penicillin were ever noted. The patient refused the newer antibiotics, which produced symptoms of severe gastric distress despite the concomitant ingestion of milk or antacids.

In addition to penicillin, many medications were given, especially bronchodilators such as epinephrine, ephedrine and aminophylline and expectorants, including ammonium chloride, syrup of ipecac, creosote and syrup of hydriodic acid. Since no evidence of tuberculosis was found on repeated examinations of the sputum and since hydriodic acid appeared to liquefy the sputum, the syrup had been given intermittently for the past 3 years. One month before the use of Neo-Penil, iodine was discontinued because the patient complained of a deep, midsubsternal burning pain in the chest after each dose. No rash, acne or other sign of iodine sensitivity had ever been noted.

On July 5, 1952, a single dose containing 1 cc. (500,000 units) of Neo-Penil was injected intramuscularly into the right buttock. A slight substernal burning similar to that experienced after iodine was noted for about 1 hour, but the patient felt better, his sputum was less tenacious, and his breathing was easier.

Three days later, a similar dose was injected into the left buttock, with a recurrence of the chest burning but subsequent improvement of his clinical condition. On July 12, a 3d injection was given into the right buttock. Suction on the syringe was carefully applied to avoid an accidental intravenous injection. No blood was aspirated before the injection.

While the patient and I were discussing the coming political conventions for about 1 or 2 minutes, he suddenly stopped talking, gasped, began to stare vacantly, stopped breathing, turned blue, stiffened, twisted over on his face in bed, had a generalized convulsion and then lay limp and apparently dead. The pulse, usually strong and easily felt, was absent. No heart beat could be heard. Aqueous epinephrine, 0.5 cc., was immediately injected into a distended neck vein and massaged toward the heart. A similar dose was given subcutaneously into the left arm. Artificial respiration was started by manual pressure over the lower chest, and after about 60 seconds the patient gasped feebly once or twice and then began to breathe. Oxygen kept at his bedside was given intermittently. For the next 30 minutes he remained comatose, gradually regaining consciousness during the next half hour. Three hours later he was fully conscious and was mentally alert enough to say, "Doctor, it is easy to die." Convalescence from this point was uneventful.

Skin tests by the scratch method, deep enough to produce slight blood, were carried out with aqueous penicillin G, Neo-Penil and syrup of hydriodic acid, resulting in negative reactions with all 3 medications. In view of the severity of the original reaction, it did not seem fair to subject him to the hazard of intradermal testing, although it was realized that this would probably have been a more accurate method for testing sensitivity.

On July 22, 10 days after the reaction, because of a low-grade fever and an apparent pulmonary infection, 5000 units of penicillin G, preceded by 0.1 cc. of epinephrine subcutaneously was administered without reaction. This was followed uneventfully by an ordinary 1-cc. (300,000-unit) dose. Approximately 15 subsequent doses have since been administered over a 6-month period without reaction.

SUMMARY AND CONCLUSIONS

A case of severe anaphylactoid reaction attributed to Neo-Penil is reported. To my knowledge it is the first such case report to appear in the American literature, although a similar case has been described in the English literature.

The course of events suggests that the patient became sensitized to iodine in the form of syrup of hydriodic acid used as an expectorant before Neo-Penil therapy and that the anaphylactoid reaction was due to the intramuscular injection of this iodine radical.

Since no anaphylactoid reaction or other evidence of sensitivity appeared to many subsequent injections of ordinary aqueous penicillin G, it is believed that the reaction to Neo-Penil was due

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†Neo-Penil is the trade name for this compound adopted by Smith, Kline and French Laboratories, Philadelphia.

not to the penicillin fraction per se but to the iodine fraction or some other component of the drug.

Deep scratch tests to Neo-Penil, penicillin G and syrup of hydriodic acid were negative. More definitive intradermal testing was not done in view of the severity of the reaction.

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Since this article was submitted for publication, a few reactions (some of them fatal) to Neo-Penil have been reported to Smith, Kline and French Laboratories.[6]

References

1. Jensen, K. A., Dragsted, P. J., Kioer, I., Nielsen, E. J., and Frederiksen, E. Leocillin (benzyl) penicillin-B-diethylaminoethylester hydriodide). *Acta path. et microbiol. Scandinav.* **28**:407-414, 1951.
2. Jensen, K. A., Dragsted, P. J., and Kioer, I. Undersøgelser over leocillinets terapeutske virking. *Ugesk. f. laeger* **113**:1039-1049, 1951.
3. Heathcote, A. G. S., and Nassau, E. Concentration of penicillin in lungs: effects of two penicillin esters in chronic pulmonary infections. *Lancet* **1**:1255-1257, 1951.
4. Ungar, J., and Muggleton, P. W. Accumulation of diethylaminoethanol ester of penicillin in inflamed lung tissue. *Brit. M. J.* **1**:1211-1213, 1952.
5. Wylie-Smith, R. Reaction to penicillin. *Lancet* **1**:1211, 1952.
6. Council on Pharmacy and Chemistry. Severe anaphylactoid and fatal reactions to Penethamate hydriodide (Neo-Penil). *J. A. M. A.* **151**:1105, 1953.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39241

PRESENTATION OF CASE

A thirty-four-year-old mechanic was admitted to the hospital because of hematemesis.

The patient had been in good health until seven years before admission, when after an automobile accident he was told that his spleen was "ruptured." He was hospitalized at that time but without definitive therapy and was subsequently discharged home. He remained well for the next five years except for episodes of upper abdominal pain and "heart burn," which occurred suddenly and without reference to meals but which he thought to be possibly associated with frequent "migraine headaches" from which he had suffered for at least ten years. The episodes of abdominal pain lasted from a few minutes to several hours and were usually severe enough to require medication. They were accompanied by numbness and tingling in the arms and hands. Two years before admission he had his first episode of hematemesis, which was massive and sudden in onset and not preceded by melena. He was hospitalized again at another hospital and continued to bleed intermittently for the next three days. He received twelve transfusions and was discharged after nine days. Five weeks later he passed a black stool. He was told at that time that he had an enlarged spleen, and splenectomy was advised after consultation with a hematologist, who did a bone-marrow biopsy. Splenectomy was carried out four months after the initial episode of bleeding. The spleen was said to have been enlarged to four times the normal size and to have shown no evidence of former rupture. Microscopical examination showed typical changes of fibrocongestive splenomegaly and a few scattered megakaryocytes, but no definite areas of extramedullary hematopoiesis. The postoperative course was complicated by an incisional abscess. The patient was discharged after seven weeks. Five days after discharge he had another episode of hematemesis that required rehospitalization and transfusions. Two weeks later after sedation for upper abdominal pain he went into shock and was rushed to the hospital, where an exploratory laparotomy was done but only a few adhesions were found. Three months later injection treatment for esophageal varices was begun, but six months afterward he required a transfusion for anemia. For the next nine months up to the time of admission to this hospital he required numerous hospitalizations and blood transfusions for hematemesis.

He denied that he drank alcoholic beverages. He thought that he had been mildly jaundiced during one of his hospitalizations. He had been rejected by the Army during World War II because of a "nervous condition."

Physical examination revealed numerous punctate angiomas over the chest and upper back. There was no icterus, and no petechiae were noted. The liver was not enlarged. Examination of the chest and abdomen was negative except for the operative scars.

The temperature was 98.6°F., the pulse 92, and the respirations 18. The blood pressure was 118 systolic, 78 diastolic.

Urinalysis was negative. Examination of the blood revealed a hemoglobin of 11 gm. per 100 cc., a white-cell count of 22,300, with 63 per cent neutrophils, 3 per cent band forms, 2 per cent late myelocytes, 1 per cent blasts, 9 per cent lymphocytes, 13 per cent eosinophils and 9 per cent basophils, and a marked increase in the number of platelets in the smear. There was slight anisocytosis and poikilocytosis and slight achromia of the red cells. The

bleeding time was three minutes; the clotting time was seven minutes in the first tube, seven minutes in the second, eight minutes in the third, eight and a half minutes in the fourth and eight and a half minutes in the fifth. There was clot retraction. The prothrombin time was 16 seconds (normal, 13 seconds). The nonprotein nitrogen was 35 mg., the fasting blood sugar 73 mg., the serum amylase 25 units, and the total serum bilirubin 0.5 mg., the total protein 7.6 gm., the albumin 5.2 gm., and the globulin 2.4 gm. per 100 cc. Bromsulfalein retention was 2 per cent. Cephalin flocculation was ++ in twenty-four and forty-eight hours. Roentgenograms on the day after admission failed to demonstrate esophageal varices, but on re-examination three days later changes consistent with esophageal varices were described. Films of the chest and abdomen failed to reveal any abnormal shadows. The two upper gastrointestinal series showed a deformed duodenal bulb, possibly the result of an old healed ulcer. The liver appeared to be moderately enlarged.

On the seventh hospital day an operation was performed.

Differential Diagnosis

Dr. Perry J. Culver*: At the first reading this appeared to be a case of portal hypertension and esophageal varices with hemorrhage. As I studied this case more closely it did not seem to be so clear cut.

May I see the films?

Dr. John F. Gibbons: On the films made during the first few days after admission the liver shadow is not apparently enlarged. The spleen, as we know, has been removed. There are no abnormal shadows in the abdomen. The gastrointestinal examination with barium reveals wide and irregular folds within the esophageal mucosa, suggesting tortuous, dilated veins. There is a small hiatus hernia that is reducible and a deformity of the superior surface of the duodenal bulb that is persistent; no ulcer crater is seen in the duodenum.

Dr. Culver: The statement was made that the liver was enlarged on x-ray examination.

Dr. Gibbons: I believe that was on a subsequent examination a few weeks later.

Dr. Edgar B. Taft: The liver appeared to be "moderately enlarged" on the second examination.

Dr. Gibbons: I think that was an error. The liver edge is at the level of the eleventh rib. In the films of the chest the heart is normal in size, with a normal-looking silhouette. There are prominent vessels in both lungs, but there is no evidence of congestive heart failure or pulmonary disease.

Dr. Culver: Is there evidence of increased hilar nodes?

Dr. Gibbons: No; I think all the shadows in the prominent right hilar region are large vessels. These are the pertinent films taken before operation.

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Dr. Culver: I have the problem of trying to decide what caused the portal hypertension and the esophageal varices. Was the disease extrahepatic or intrahepatic? Aside from the possibility that the episode of shock was due to the ill effects of medication on a sick liver, I can find little to suggest that this man had a primary disease of the liver to explain the development of the portal hypertension and esophageal varices. Also, I think I can rely on the liver-function tests, which were negative. Having disposed of the liver as the cause of portal hypertension, I am left with the problem of the extrahepatic causes of portal hypertension. The spleen as described was apparently of the type seen in Banti's syndrome, and its appearance certainly could have resulted from a thrombotic episode involving the portal system — the splenic vein or the portal vein. The episodes of upper abdominal pain may have been caused by some recurrent thrombotic or phlebitic episodes involving the portal-vein bed.

What disease might involve the portal-vein bed? There is a condition, the cause of which is unexplained, that we call chronic recurrent thrombophlebitis of the portal-vein system. I personally visualize the process as one of progressive thrombophlebitis in the portal bed. We have seen a few cases here. The patients usually have repeated episodes of hematemesis, and abdominal pain; they have splenomegaly without serious involvement of the liver until the disease has progressed for a long time. These patients have had multiple operations for hematemesis, and so far some of them are alive after a long time.

I should like to know if the blood-cell picture was abnormal before splenectomy. I should also like to know about the platelet count, which I assume was somewhat low before splenectomy and rose afterward, and particularly about the white-cell count before splenectomy. I suppose it too was low.

I must consider diseases of the reticuloendothelial system, diseases of the lymphatic system and diseases of the supporting structures of the spleen. I am most impressed with the eosinophil count of 13 per cent. This attracted my attention when I first read the case report, and I have had difficulty disregarding it ever since. As a matter of fact my deliberations have centered around that eosinophilia. What generalized conditions could involve the spleen, possibly involve the portal bed and produce eosinophilia? There is, among the collagen diseases, polyarteritis nodosa; but this patient had no urinary-tract involvement and no hypertension.

A disease of the lymphatic system that I should like to consider seriously is Hodgkin's disease. Hodgkin's disease notoriously can be slowly progressive, can certainly cause an eosinophilia and can involve the spleen and the retroperitoneal lymph nodes. It may produce pain in the middle of the abdomen and may be associated with throm-

bophlebitic phenomena in the portal system. The only difficulty with such a diagnosis is that no enlarged lymph nodes were described. We do not have to see enlargement of peripheral lymph nodes, but I should be much happier in making that diagnosis if the abdominal or mediastinal lymph nodes had been enlarged.

One of the infiltrative diseases like Gaucher's disease could have caused splenomegaly and might have involved the lymph nodes. I think that would have been diagnosed in the spleen at splenectomy. It is not associated by and large with eosinophilia, and I do not think I have to consider it very seriously. The other lymphoid diseases do not have to be considered at all.

In passing one has to think of leukemia, as a generalized systemic disease that may have involved the spleen and produced an abnormal blood picture. This patient's blood picture was not too abnormal, although I suppose a low-grade leukemia may have been present. I should like to see a few more band forms and myelocytes or metamyelocytes to make a diagnosis of leukemia.

To come to a sharper focus on what is wrong, I shall have to decide what generalized systemic disease could have involved the spleen, caused the eosinophilia and secondarily resulted in portal-bed thrombosis and esophageal varices. The only one that I can make fit such a category is either Hodgkin's disease, in spite of the absence of lymphadenopathy, or an unexplained type of thrombophlebitis involving the portal bed, with splenomegaly, portal hypertension and esophageal varices without liver disease. The latter, however, would not be expected to produce an eosinophilia. So, pinning my faith on the eosinophil count, I am going to say that this man had Hodgkin's disease, thrombosis of the portal system, esophageal varices and perhaps some Hodgkin's infiltration of the liver but no primary liver disease. The operation may have been a transthoracic approach for ligation of esophageal varices or possibly a liver biopsy.

Dr. Daniel S. Ellis: Where did you think the thrombus was? Was it intrahepatic or extrahepatic?

Dr. Culver: I think there may have been multiple thrombi all through the portal system; I should not want to place a thrombus in any one place.

Dr. Bernard M. Jacobson: How could you make a diagnosis of Hodgkin's disease if the spleen did not show it?

Dr. Culver: It may not have been in the spleen at the time of splenectomy. It may have been only in the retroperitoneal tissue.

Dr. Taft: Do you think that the accident seven years before entry had anything to do with the difficulty?

Dr. Culver: I do not think so.

Clinical Diagnosis

Extrahepatic portal hypertension, with bleeding esophageal ulcers.

Dr. Perry Culver's Diagnoses

Hodgkin's disease, with ? infiltration of liver.
Thrombosis of portal system.
Esophageal varices.

Anatomical Diagnoses

Thrombosis, old, portal vein, with esophageal varices and (congestive splenomegaly).
Myelogenous leukemia or myeloid hyperplasia of bone marrow, severe.
[Deficiency of serotonin (vasoconstrictor substance).]

Pathological Discussion

Dr. Taft: This patient had a very complicated course. At the first operation a splenorenal shunt was attempted but was unsuccessful. A portacaval shunt was considered, but there were so many adhesions about the porta hepatis binding loops of small bowel to this area and to the previous transverse operative incision that this likewise could not be done. After the exploratory abdominal incision had been closed, the thorax was entered, and 3 large columns of esophageal varices were sutured. An old subdiaphragmatic blood clot was evacuated. There was speculation that this might have been the cause of the elevated white-cell count. A liver biopsy taken at this time was not remarkable.

The patient's subsequent course in the hospital was prolonged and complicated by sepsis and eventually terminated fatally approximately four months after admission. We shall return to this history in a moment. First I should like to present the autopsy findings relevant to our discussion thus far.

The portal venous system was most interesting. The portal vein measured 2 cm. in diameter and was completely obstructed in an unusual fashion. There was a cord-like structure occupying most of the lumen, with complete obstruction of the branches to the liver and of the splenic and mesenteric veins at their points of entrance into the portal vein. Thus, the portal vein was completely occluded. One might speculate that this had been a gradual process, perhaps initiated by trauma associated with the automobile accident and resulting in splenomegaly and esophageal varices. The hepatic artery was markedly dilated and measured 2 cm. in circumference. I was hoping that Dr. Culver would agree that this might have been associated with the automobile accident because this seemed to me to be the most likely cause of the thrombosis. I think that the scar tissue found at operation about the porta hepatis by Dr. Robert R. Linton certainly could have been the result of trauma and that the deformed duodenal cap described radiologically was

associated with this focal scarring. I think Dr. Culver's comparison of this history with those of patients having chronic recurrent thrombophlebitis of the portal venous system is quite apt.

DR. CULVER: Dr. Taft, you still have not answered the fundamental question, which is why the patient had portal-bed thrombosis.

DR. TAFT: I do not have any other suggestions than that the portal-vein thrombosis must have been gradually progressive and that it may have been initiated by trauma.

To continue this unfortunate man's history: the white-cell count rose after these first two operations and remained between 40,000 and 55,000, with a differential not too unlike the one given in the protocol. A bone-marrow aspiration revealed that the marrow was very cellular, with a myeloid-erythroid ratio of 18:1. The patient continued to require transfusions for what was interpreted as slow intestinal bleeding, but he was finally discharged to a nursing home thirty-six days after admission.

He was readmitted four days later because of hematemesis. At this time the bleeding time was found to be more than twelve minutes. A prolonged bleeding time had been noted at another hospital previously, but the first observations here were as reported. This patient was studied extensively on this account by Dr. Frederick S. Bigelow, of the Thorndike Memorial Laboratory at the Boston City Hospital, and Dr. Frank H. Gardner, of the Peter Bent Brigham Hospital. In addition to his elevated white-cell count, the patient had platelet counts ranging between 4,300,000 and 6,200,000 and a most peculiar abnormality in that the serum and apparently the platelets were deficient in vasoconstrictor content. Such a deficiency may explain the prolonged bleeding time observed.

Treatment with cortisone produced some improvement in the bleeding tendency. The patient continued to bleed from the gastrointestinal tract, however, and required many transfusions. On the fortieth day of the second admission a fundicectomy of the stomach was done. The postoperative course was complicated by jaundice, peritonitis and the development of a fistula from the stomach to the skin wound. The patient died on the forty-first postoperative day after a febrile course with temperatures spiking to 105°F. during the last week of life.

At autopsy the septic terminal course of the patient was explained in part by an acute bacterial endocarditis of the aortic valve. Other sites of infection were focal areas of peritonitis and a thrombophlebitis of the right cephalic vein. There were numerous infarcts in the kidneys and liver, and two moderately large pulmonary emboli were found.

There was no evidence of extramedullary hematopoiesis in any organ. The bone marrow was red and grossly normal. Microscopical examination showed enormous numbers of megakaryocytes. The bone marrow was extremely hyperplastic, with a preponderance of immature white blood cells and blasts. Erythropoiesis was still present but diminished in amount. It is my opinion that this represented an early myelogenous leukemia. I must admit, however, that the picture in the bone marrow could have been the result of extreme hyperplasia, which did not necessarily represent a malignant change. Certain features of the clinical picture, however, — the thrombocytosis and the eosinophilic and basophilic leukocytosis, — I cannot explain on the basis of an extreme leukemoid reaction to repeated blood loss and infection. As for the possibility that splenectomy produced this sort of picture or a thrombocythemia, the only report I know of, which was referred to by Dr. Bigelow, is that of Ek and Rayner,[1] who analyzed the hematopoietic picture of 18 patients after splenectomy for unrelated causes. They found no evidence of increased platelets or of markedly increased white-cell counts or of any of the other changes that one might suppose could occur.

I wonder if Dr. Gardner would tell us about the peculiar bleeding tendency exhibited by this patient.

DR. FRANK H. GARDNER: I think that many pathologists might disagree with the observations of Ek and Rayner. A postoperative rise in platelets after intentional or incidental splenectomy is certainly to be expected, but I do not know of any platelet counts in the range of 4,000,000 to 6,000,000 that persisted after splenectomy, as was observed in the case under discussion.

I can appreciate Dr. Culver's difficulty in making a diagnosis of leukemia in this patient. When I first saw him I believed that the diagnosis was probably chronic myelogenous leukemia. I had expected that more proof of tumor would be demonstrated at post-mortem study. It should be remembered that severe fulminating infections may alter the response of leukemic infiltration. Heinle and Weir[2] reported a case of leukemia followed for about five years in which the end result was almost total abolition of leukemic infiltration in organs at post-mortem examination. Terminal infection may explain why so little evidence of leukemia was present. I do not think that we can exclude the presence of a leukemoid reaction in this patient, however.

Of course, the interesting problem for us was the bleeding tendency. Dr. Linton commented that there was a marked amount of oozing when the tissue was handled and that the adhesions seemed to bleed excessively. After the patient returned from the convalescent home a prolonged bleeding time was found by most observers. This bleeding tendency may well have contributed to the frequent gastrointestinal hemorrhages. The studies that Dr. Bigelow was kind enough to carry out were of con-

siderable interest and might be applied to other patients to determine if another physiologic defect might exist in platelets. As Dr. Taft mentioned, the purpose of those observations was to determine whether or not the serum of the patient had serotonin or the vasoconstrictor factor for an ox artery. All normal persons have this vasoconstrictor factor. It is not found in plasma but in clotted blood; for that reason it is assumed to be either produced or augmented by the lysis or destruction of blood platelets. This patient's clotted blood, even with this tremendous platelet count, gave no evidence of the vasoconstrictor substance. I do not think that the relation of these observations to the clotting mechanism can be estimated because similar studies have been limited to date.

We have had an opportunity to transfuse blood platelets from 2 such patients with enormous platelet counts. In both we observed an expected normal platelet survival of four to six days. However, the yield of platelets after the transfusion was extremely small. Because of the tremendous megakaryocytic hyperplasia we have wondered if these platelets might be immature. Certainly other studies such as platelet adhesiveness and fragility should be carried out to try to define the function of the platelet more carefully.

Dr. Jacobson: It is difficult to make a diagnosis of myeloid metaplasia in such a patient as this. When I first saw the patient, I thought that that might be what he had. Now I should call it something less definite — namely, what Dameshek[3] has called a "myeloproliferative syndrome," or excessive formation of white cells and platelets with a secondary bleeding tendency. There are intangible gradations between this type of myeloid proliferation and myeloid metaplasia. The findings in the bone marrow and peripheral blood are very similar; only the organ involvement is different. It is, of course, related to myeloid leukemia, but I suspect that in leukemia one ought to find infiltrations in the liver and spleen.

Dr. Taft: Leukemia may histologically be limited to the bone marrow and peripheral blood although this is admittedly a rare circumstance.

Dr. Culver: Did the patient under discussion have the thrombocytosis before he had the splenomegaly?

Dr. Jacobson: I suspect that the thrombocytes were very high then.

Dr. Taft: Except for the terminal episodes associated with thrombophlebitis in the cephalic vein and endocarditis of the aortic valve he had no evidence of a long-standing thrombotic tendency. There were no thrombocytic thrombi such as are seen in idiopathic thrombocytopenic thrombosis.

Dr. Culver: Was there any enlargement of retroperitoneal lymph nodes?

Dr. Taft: No.

Dr. Robert R. Linton: I should like to make one comment about this type of patient. Aside from the fact that from the clinical point of view this was a most puzzling case and, as one can see from the protocol, presented an extremely difficult problem, both in diagnosis and in treatment, the most important thing is that in my opinion a splenectomy should never have been done. Under any conditions a splenectomy is a poor therapeutic procedure for the treatment of bleeding esophageal varices, because, as in this case, it may preclude a satisfactory portacaval shunt. Unfortunately, many surgeons are still performing splenectomies for bleeding esophageal varices, and we see not a few of these cases in our hospital, most of which are just as tragic as this case proved to be. I have often made the statement that a surgeon should never do a splenectomy under these conditions, unless he is prepared to do a splenorenal venous anastomosis at the same time, because this may be the only chance to create a satisfactory portacaval shunt. I should like again to reiterate and re-emphasize that statement.

References

1. Ek, J. I., and Rayner, S. Analytical study of splenectomised cases after traumatic rupture of healthy spleen. *Acta med. Scandinav.* **137**:417-435, 1950.
2. Heinle, R. W., and Weir, D. R. Morphologic obliteration of chronic myeloid leukemia by active tuberculosis. *Am. J. M. Sc.* **207**: 450-453, 1944.
3. Dameshek, W. Some speculations of myeloproliferative syndromes. *Blood* **6**:372-375, 1951.

CASE 39242

Presentation of Case

A fifty-six-year-old housewife entered the hospital complaining of shortness of breath and pains in the right leg for two years.

At the age of ten the patient was kept in bed for a short time; she had no joint symptoms nor chorea but had a skin rash at the time. After this, a physician told her that she had had rheumatic fever. Later she became short of breath after mild exercise and was unable to play games with other children. In the years that followed, however, she enjoyed fair health and had a normal pregnancy. Nine years before admission she had an attack of pleurisy, which was accompanied by fever and chest pain. She was kept in bed for three months, and since that time she had never been free of shortness of breath on exertion. Shortly after this, she had a sudden episode of shortness of breath with paroxysmal nocturnal dyspnea. She was treated with digitalis for a period of two years. Episodes of shortness of breath, orthopnea and dyspnea occurring at night were present intermittently until admission. These were made worse by intercurrent colds. She took digitalis sporadically when the shortness of breath was worse. During this time she noted episodes of palpitation and skipped beats as well as excess perspiration and night sweats, and hyper-

tension was discovered four years before admission. For approximately two years she complained of numbness with pain in the right leg that radiated to the lower calf, was brought on by exertion and disappeared with rest. The right leg generally felt cooler than the left. This condition had severely limited the patient's activity and she had hardly left the house for years since walking on the street was too painful. She denied past phlebitis. Three months previous to admission a cough and persistent cold developed with marked exacerbation of the shortness of breath. She was treated with sedation and pronestyl, with a good response; digitalis was not continued because of a toxic reaction of undetermined nature. At this time quinidine was started. A roentgenogram was reported as showing enlargement of the heart; the basal metabolic rate was +31 per cent, and the blood cholesterol was 145 mg. per 100 cc.

FIGURE 1. *Roentgenogram of the Chest. Arrows point to the shadow of the enlarged left atrium.*

The patient denied having had hemoptysis, peripheral edema, abdominal swelling, chest pain, fainting and convulsions.

Physical examination disclosed an anxious, perspiring woman in no acute distress. There was increased prominence of both eyes, with a staring appearance and definite lid lag. Convergence was slightly impaired. The fundi were normal. The thyroid gland was not enlarged. The heart was enlarged, the left border being percussible at the anterior axillary line in the sixth interspace. The rhythm was grossly irregular. The aortic second sound was greater than the pulmonic, and the mitral first sound was not accentuated. There was a Grade 2 rumbling mid-diastolic murmur well localized to the apex. There was no peripheral edema. All the pulses in both legs were absent, and the skin of the legs was cool. The hands were warm and moist, with a slight tremor.

The temperature was 98.6°F., the pulse 84, and the respirations 24. The blood pressure was 160 systolic, 120 diastolic, in the left arm and 180 systolic, 110 diastolic in the right. The blood pressure in the legs was unobtainable.

The urine had a specific gravity of 1.012; the sediment contained 6 white cells and many epithelial cells per high-power field. Examination of the blood revealed a hemoglobin of 15.5 gm. per 100 cc. and a white-cell count of 11,200, with 76 per cent neutrophils, 20 per cent lymphocytes and 4 per cent monocytes. The hematocrit was 47 per cent. The blood Hinton test was negative. The basal metabolic rate was —13 per cent, the protein-bound iodine 5.2 gamma per 100 cc. and the uptake of radioactive iodine 38.7 per cent after forty-eight hours. An electrocardiogram disclosed auricular fibrillation at a rate of 80 per minute, a QRS interval of 0.09 second in the limb leads and 0.11 second in the chest leads, and T waves that were in-

FIGURE 2.

verted in Leads aVR, V_1, V_2, V_3 and V_4 and low in Lead aVL.

Roentgenograms of the chest were interpreted as showing congestion of pulmonary vessels. There was marked enlargement of the left atrium and some enlargement of the ventricles, predominantly the left (Fig. 1 and 2). A small diverticulum of the esophagus was demonstrated at the level of the tracheal bifurcation. No arterial calcification was present in films of the lower abdomen and legs.

The patient was treated with a low-sodium diet and digitoxin. She was comfortable in bed but complained of pain in the right leg when she walked about. On the morning of the fourteenth hospital day, she was found dead in bed.

Differential Diagnosis

Dr. Edward Hamlin*: At first sight this hardly appeared to be a surgical problem, and I wondered if I had been given the right protocol. It would appear more appropriate for a cardiologist to deal with it. If someone can explain the electrocardiographic findings, I shall see what I can do.

Dr. Alfred Kranes: The electrocardiogram was noncontributory if that will help you any.

Dr. Hamlin: May I see the x-ray films?

Dr. Stanley M. Wyman: The films of the chest demonstrate a heart that is greatly enlarged. The enlarged left atrium can be well seen through the central portion of the heart shadow, and this is also well demonstrated in the lateral view displacing the esophagus posteriorly (Fig. 1 and 2). About the enlargement of the other chambers, I do not think I can be too specific; probably all chambers are involved. There is definite pulmonary vascular engorgement and bilateral pleural effusion. I see no evidence of intracardiac calcification, but since the films are not heavily penetrated this might be overlooked.

Dr. Hamlin: That does not help me at all. I want to get away from the heart.

Dr. Wyman: I do not have the films of the legs and abdomen that were described.

Dr. Hamlin: The first consideration about the type of heart disease is that it was based on an old rheumatic infection; the enlargement of the left atrium and the report of the auricular fibrillation certainly make that a primary consideration.

Dr. J. H. Averill: I saw this patient on the ward so perhaps I can clear up the question of the heart disease. She had a good history for rheumatic fever; she had a history of repeated pulmonary episodes, paroxysmal nocturnal dyspnea and so forth, an apical diastolic murmur and an enlarged left atrium. The electrocardiogram showed auricular fibrillation, with inverted T waves in Leads V_1, V_2, V_3 and V_4. Our opinion on the ward was that she had mitral stenosis with a moderate amount of congestive heart failure.

Dr. Hamlin: This patient with rheumatic heart disease and hypertension of long chronicity and giving the impression in some of these attacks of possibly having pulmonary emboli, was fibrillating and may have had thyrotoxicosis as a contributing feature of the fibrillation. The thyrotoxicosis was obviously ruled out by the protein-bound iodine and the radioactive-iodine uptake. The only problem that I can help out on is the peripheral circulation. The patient had pain and numbness in the left leg for two years, which I presume was increasing during that time to some extent. Findings on physical examination other than those of the heart were singularly absent except for the absence of all the pulses in both legs and the coolness of the skin of the legs. Does the note that all the pulses in the legs were absent include the femoral arteries? I assume that the popliteal and pedal pulses were absent.

Dr. Farahe Maloof: The pulsations in the femoral arteries were absent.

Dr. Hamlin: All the vessel pulsations were absent. In a patient with symptoms like this patient's the most important information from the surgical point of view is the description of the collateral circulation. I should like very much to know what would have happened if the legs had been elevated? How quickly would they have blanched? Would the veins have emptied equally rapidly in both legs? What appearance would they have had on dependency after two or three minutes? All this would be of considerable importance in the prognosis of the peripheral vascular disease.

Dr. Patricia A. McIntyre: There was no change in the color of the right leg on either elevation or dependency; it was blanched, and there was no venous filling in either position.

Dr. Hamlin: Did she show resting pain? That is extremely important. When patients have resting pain with arterial insufficiency, it is an ominous sign indeed.

Dr. Kranes: When she walked for some distance she had pain; the pain might continue for half an hour to three-quarters of an hour after she stopped walking.

Dr. Hamlin: There was intermittent claudication. When I use this term, I always remember Dr. John Homans, Sr., who used to become very upset because no one knew what claudication meant; it means limping. As commonly used, therefore, it is a misnomer; these patients do not limp; they stop to rest. The patient then had arterial insufficiency of a major degree, particularly in the right leg; the major vessels apparently were completely obliterated, but she had enough collateral circulation to keep the legs alive at least under resting circumstances. This means that whatever

*Associate visiting surgeon, Massachusetts General Hospital.

produced the arterial insufficiency was of long enough duration to build up collateral circulation. The causes of arterial insufficiency are not too many. Arteriosclerosis is by far the most common cause, and she may well have had it. She had hypertension and undoubtedly had some arteriosclerosis. We are given one other fact that she had insufficient arteriosclerosis of the calcific variety to produce a shadow in the x-ray films so that she did not have the typical pipe-stem arteries of the aged or of diabetic patients. After all, she was only fifty-six. That, however, does not rule out arteriosclerosis as a cause of the arterial insufficiency. She may have had Buerger's disease. Buerger's disease in women is a rare disease indeed; in this hospital it has occurred in 1 patient out of 100 with peripheral vascular disease. Moreover, there was no past history of phlebitis, which is a concurrent incidental finding — particularly the migrating phlebitis. I think I can rule out Buerger's disease.

Emboli will cause arterial insufficiency. The typical embolus to the periphery is a sudden overwhelming affair, which draws attention to itself in no uncertain terms. It is possible for showers of small emboli to go to the periphery over a long period and thus to obliterate the major arteries and to stimulate the collateral circulation to develop.

It seems most likely that pulmonary emboli would best explain some of the pulmonic attacks that this patient had, particularly the one that was described as pleurisy. We know that pulmonary emboli are more common in cardiac patients than in any others. To discuss pulmonary emboli one has to discuss the site of origin to some extent, the most common being the legs. There was no history of phlebitis in the past nor any indication that she had phlebitis at any time during the final illness. Therefore, it seems reasonable to eliminate that although it is not necessary with an acute pulmonary embolus from the legs to demonstrate any local evidence of origin whatsoever.

Could she have had emboli from the heart through a patent septum? There is nothing as far as I know against that possibility. I should like to make this extraordinary diagnosis of embolic disease from the atrium not only to the periphery but also to the lung through a patent septum, but I do not know enough to make that diagnosis. The possibility that the peripheral disease arose from clots in the aorta seems less likely than emboli from the heart in this case although it is a much more common cause of arterial insufficiency of the periphery. The patient was quite young for plaques pulled off from the aorta to obliterate the circulation over a long enough period to produce the collateral circulation. I think I should eliminate that also.

I have talked a great deal and arrived at no conclusion. I think I shall say that this patient had emboli to the femoral and iliac arteries, with subsequent thrombosis over a sufficiently long period to produce the extraordinarily good collateral circulation, and that the cause of death and the origin of the impairment of peripheral circulation was the heart. This has been described by Leriche[1] and others, though almost always as occurring in males and producing impotency.

DR. MALOOF: You said that the greatest percentage of emboli go to the extremities. Your surgical colleagues, Drs. Warren and Linton,[2] state that 64 per cent of emboli go to the limbs; and in another article emanating from the medical service of this hospital[3] the greatest percentage, about 50 per cent, of emboli are said to go to the brain. What is the reason for the discrepancy?

DR. HAMLIN: I am sure they are not using the same cases. Dr. Linton is talking about surgical cases, and the internists are talking about medical cases.

DR. BENJAMIN CASTLEMAN: How frequently do pulmonary emboli come from leg-vein thrombi in patients who have had peripheral arterial occlusions?

DR. HAMLIN: I cannot quote figures; pulmonary emboli may come from the legs with arterial occlusions but not frequently. They commonly occur postoperatively after amputation of the legs. Of course, there is an added factor — the tying off of the femoral veins, which may produce stasis and origin for emboli. Actually I think that we see relatively few in patients with arterial insufficiency who are walking around.

DR. CASTLEMAN: I would have supposed that an embolus to the lung from the leg veins is more likely than from a heart with a defect of the interatrial septum.

DR. HAMLIN: I should judge from my experience that it would occur equally frequently from both sources.

DR. JACOB LERMAN: The patient was studied for thyroid disease, because the service was interested in the fact that she had exophthalmos and she also had a high basal metabolic rate. It was my own impression that she had familial exophthalmos. It was finally proved that she did not have hyperthyroidism.

DR. KRANES: I should like to ask Dr. McIntyre if the protocol is correct; did the pain in the leg come on suddenly?

DR. MCINTYRE: Two years before admission the patient stated that she had sprained her right ankle, by which she meant the sudden onset of pain in the ankle while walking. She rested for several days; thereafter she noted that as she walked a numb feeling around the right ankle developed, extending up the right leg; if she continued to walk, the entire right leg became extremely painful. Long periods of rest gave relief. There was never any similar pain in the other leg.

Clinical Diagnoses

Rheumatic heart disease, with mitral stenosis.
Saddle embolus of aorta.

Dr. Edward Hamlin, Jr.'s Diagnoses

Rheumatic heart disease.
Peripheral emboli of long duration.

Anatomical Diagnoses

Rheumatic heart disease, with mitral and aortic stenosis.
Thrombus, left atrium, with probable ball-valve occlusion of mitral valve.
Embolus of abdominal aorta, iliac and femoral arteries, organized.

Pathological Discussion

Dr. Castleman: Obviously, we asked Dr. Hamlin to discuss this case from the peripheral vascular standpoint rather than to discuss the cardiac problem because one would not be able to predict the cause of the patient's death from the clinical history. She had a large rheumatic heart (weighing over 400 gm.), a severe mitral stenosis and a mild aortic stenosis. Within the large left atrium was a large thrombus, which at the time of autopsy was not attached, but was lying free (Fig. 3). This thrombus, I believe acted as a ball valve and was the cause of death by obstructing the mitral valve; at least that is the only explanation we could find for her sudden death. I do not believe the thrombus had been lying free before the terminal episode because in addition we found mural thrombi in several parts of the atrium. It is quite probable that the ball-valve thrombus had been attached up to the time of her sudden death because she had no previous history of attacks of syncope that might suggest ball-valve occlusions. These mural thrombi formed the source for the embolism to the bifurcation of the aorta and to all its branches — both common iliac arteries, external and internal, and the femoral arteries on both sides were occluded (Fig. 4). The latter occlusions were very old, organized, recanalized and somewhat fibrotic, without any evidence of fresh thrombus. It certainly must have been an embolus with superimposed thrombosis that, as Dr. Hamlin suggested, probably extended down to the arteries and built up the occlusion over the years. I cannot tell at this stage whether the embolus had been present for two years or ten years. It may have occurred at the time of the sudden pain in the ankle two years previously.

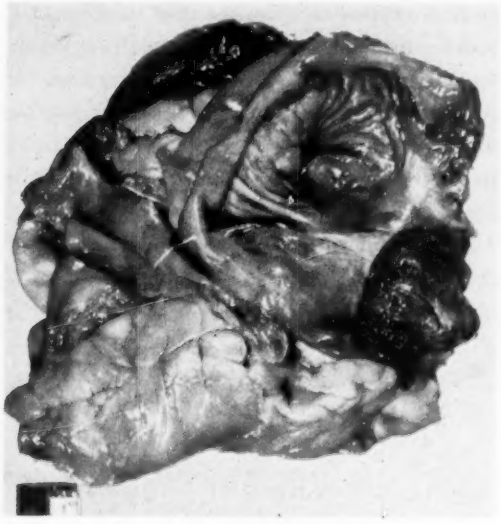

Figure 3.

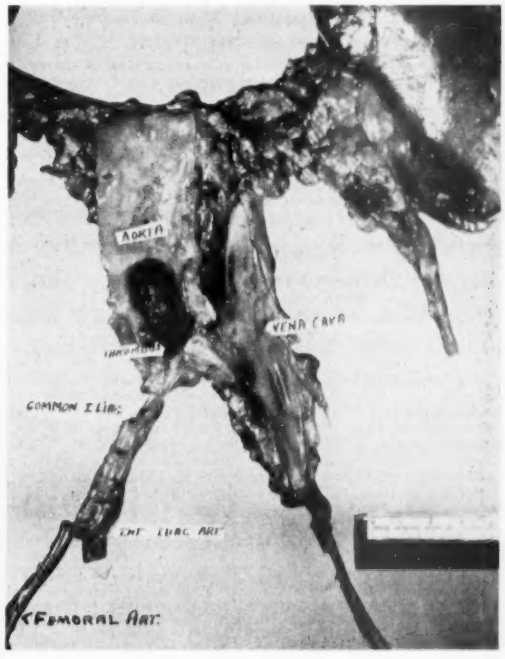

Figure 4.

A Physician: What did the lungs look like?

Dr. Castleman: The lungs contained no evidence of previous infarction; we were unable to see even a scar of an old infarct. There was little congestion and nothing that seemed to point to old emboli; the pulmonary arteries were all free.

References

1. Leriche, R. De la résection du carrefour aortico-iliaque avec double sympathéctomie lombaire pour thrombose artéritique de l'aorte; le syndrome de l'oblitération termino-aortique par artérite. *Presse méd.* **48**:601, 1940.
2. Warren, R., and Linton, R. R. Treatment of arterial embolism. *New Eng. J. Med.* **238**:421-429, 1948.
3. Daley, R. Mattingly, T. W., Holt, C. I., Bland, E. F., and White, P. D. Systemic arterial embolism in rheumatic heart disease. *Am. Heart J.* **42**:566-581, 1951.

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RESEARCH IN GENERAL PRACTICE

AN address on "Opportunities for Research in General Practice," delivered before the Section of General Practice of the Manchester Medical Society by Robert Platt, M.D., professor of medicine at the University of Manchester, may be found in the *British Medical Journal* for March 14, 1953.

Commenting on the paucity of articles by general practitioners, at least in the foremost British journals, Professor Platt attributes this dearth to a common misconception of what constitutes research, and the type of person who does it. Research has come to represent, in the mind of the full-time practitioner, a multiplicity of laboratory tests with results to be measured by the buret or the calorimeter and calculated with a slide rule, to the exclusion of a series of simple but accurate observations on living material evaluated by an experienced and open mind. He believes that he is thus eliminated from the field.

With the realization that a proportion of the research undertaken is designed by some of those engaged in it not for learning or for teaching but to advertise the diligence of the individual—a standard to which the universities have contributed not a little — the competent practitioner, occupied with his own affairs and lacking the necessity of employing this means of intellectual communication, is inclined to neglect the resources that he has so close at hand. He forgets the research value of the clinical material with which he is surrounded, the proper study of which constitutes as high an order of medical investigation as has ever been made. He perhaps overlooks the fact that the most valuable contributions to medical knowledge have flowed from generation after generation of general practitioners since Hippocrates first described disease, and taught the art of observation. From that time, when medicine first became a profession based on the skilful interpretation of sound observation, its development has been in the hands of the general practitioners. For most of the searchers after knowledge, wherever this particular interest may have lain, have had to earn their bread in general practice.

Galen, for all the errors that he passed on to posterity, was an ingenious and indefatigable investigator who discovered the functions of nerves and insisted that the blood was in motion, even if not in circulation. Personal physician to the gladiators at Pergamos at the beginning of his career, he soon became the most illustrious practitioner in Rome.

Practicing Arab physicians laid the foundations of modern chemistry and pharmacology and gave to science the technics of distillation, crystallization and sublimation; Avicenna observed that "if a patient makes movements with his hands as if picking things off himself, it is a sign of death," Vesalius, the father of anatomy, and Paré, the father of surgery, were general practitioners in addition to their anatomic and surgical skills, and William

Harvey was in his day physician to St. Bartholomew's Hospital.

Nathaniel Hodges, who had followed his family practice in London in the dreadful year 1665, left the best clinical description of the last of the great plagues; Auenbrugger percussed his patients after practicing the maneuver on a barrel, and Laënnec's first stethoscope was devised to study the muffled sounds that physiology still creates within the narrow confines of the living clay. The researches of Withering and Jenner represent the peaks of investigative productiveness to which general practitioners have risen, but a steady procession of contributors has succeeded them — Hezekiah Beardsley, of Connecticut, who recognized and described pyloric stenosis in the infant; Ephraim McDowell, the backwoods surgeon and family doctor, with his eight successful ovariotomies; William Beaumont, the army doctor, who drew no one knows how many hogsheads of gastric juice from his living sideshow, St. Martin; Sir James Mackenzie, the family practitioner turned cardiologist; William Pickles, still the distinguished rural epidemiologist of Wensleydale, and countless others.

General practice having fallen, it was once hinted, into disrepute, is again on the upsurge. But it has always been the responsibility of general practice to keep the faith of the physician and in many ways to maintain unbroken his line of service to the community. It is also the function of the practitioner, like the master of the ship lost in the great outflow of the Amazon, to let down his buckets where he is and tap the fresh sources that surround him.

In opportunity for the description of disease and the study of its effects, for the appraisal and improvement of methods of treatment, for simple statistical analyses and for practical research into medical economics, the distribution of medical care and the relations between physician and patient, the position of the general practitioner remains unique.

FATAL REACTIONS TO PENICILLIN

THE Council on Pharmacy and Chemistry of the American Medical Association recently released a report of severe anaphylactoid and fatal reactions to penethamate hydriodide (Neo-Penil)* of which the case reported by Chotkowski elsewhere in this issue of the *Journal* is an example.† Penethamate is the name given to the diethylaminoethyl ester of penicillin G, the hydriodide salt of which is known by the trade name, Neo-Penil. This repository type of preparation is unique in that it has a special affinity for lung tissue, suggesting that it may have some special virtue in the treatment of pulmonary infections caused by penicillin-sensitive organisms.

Severe reactions and even deaths from penicillin, particularly from procaine penicillin preparations, have now been recognized as hazards of this therapy; fortunately, such reactions are extremely rare considering the widespread use of the antibiotic in various forms. However, the report of the Council indicates that in a period of six months 14 severe anaphylactoid reactions, including 3 that resulted in death, followed the administration of penethamate hydriodide. These reactions appeared to be similar to those previously described as anaphylactic-like shock and convulsive reactions due to penicillin or procaine hypersensitivity. It is possible that inadvertent injection into a vein was a contributing factor, at least in some of the cases. Muscular twitching and convulsive seizures, however, were more frequent, occurring in 11 of the 14 patients. In 9 patients the reaction occurred almost immediately or within five minutes of injection, but in 1 case convulsive seizures began ten hours after the administration of the drug.

The interesting feature of this report is that all its essential information was the result of a survey initiated, conducted, recorded and made available by the pharmaceutical firm that produces and distributes the product in this country. Moreover, the firm, without waiting for the action of the Council, was quick to notify physicians of the hazard and of the possible ways of minimizing this hazard at least to some extent.

In the introduction to the Council's report attention is called to the fact that a calculated risk is taken whenever one prescribes or administers a

*Council on Pharmacy and Chemistry. Severe anaphylactoid and fatal reactions to penethamate hydriodide (Neo-Penil). *J. A. M. A.* **151**:1105 1953.

†Another report of a severe, nonfatal reaction to penethamate hydriodide has been received and will appear in a later issue of the *Journal*.

potent therapeutic agent. The degree of risk varies considerably with the particular drug involved and the condition of the patient. A useful drug should not be avoided or condemned simply because it occasionally causes serious reactions. It is also noted that responsible pharmaceutical firms recognize their obligation to inform physicians of any serious side effects of their products. There have been other recent examples of the discharge of this responsibility by pharmaceutical firms. The Council offers to Smith, Kline and French Laboratories a well deserved commendation for voluntarily furnishing the information that formed the basis of its report and also for its prompt action in notifying the medical profession.

"THE POMP OF YESTERDAY"

No planning of an annual meeting of the Massachusetts Medical Society is permitted to reach the stage of efflorescence without an editorial *ave* and none is allowed to pass into history without some sort of valedictory pronouncement. So let it be with the hundred and seventy-second consecutive gathering of the clan, which took place last month at the Hotel Statler, in Boston, with 2240 fellows and guests in attendance.

Many of the details of the program have already been previewed and need not be repeated here; always important is the annual meeting of the Council, occurring on the evening before the show opens under the big top. On this occasion harmony reigned supreme, even the most contentious councilor finding it difficult to stir up an argument over an agenda that had been prepared with so much thought by the working committees and considered so carefully by the executive councilors.

Some debate took place over the report of the Subcommittee on Accident and Health Insurance of the Committee on Public Relations regarding the type of policy that might be written and the insurance carrier selected. The committee was authorized to explore the possibilities further.

The Committee on State Legislation reported the study of no less than 198 bills affecting the public health or the practice of medicine introduced into the current session of the Legislature. Of the particularly controversial subjects the fluoridation of water supplies had been recommended for further study and a new Regional Health Districts law had been drafted to replace the present Union Health Department law. This will become the subject of further consideration.

The report of the Committee on Public Health, having to do largely with multiphasic screening clinics, was discussed at some length and finally elicited an expression of opinion of the Council in opposition to further screening clinics as conducted by the Massachusetts Department of Public Health, at least until some final decision on their value is reached. The Subcommittee on Mental Health had considered a request for information about whether psychiatrists should make a charge for their services to physicians and their dependents. The decision was against such a charge, but in view of the occasionally protracted nature of these services, it was recommended that some sort of financial arrangement might be made. The matter was referred back to the subcommittee for further study.

Certain important changes in the *By-laws* were adopted at the annual meeting of the Society, taking place the day following the Council meeting. Fellows over sixty-five who had formerly, on request, become retired fellows with remission of dues now become senior fellows, with all privileges and still with remission of dues. Delegates to the American Medical Association shall now be nominated by the Committee on Nominations or from the floor, instead of by the President (or from the floor); certain changes were made in the status and duties of the Secretary in relation to committees, and a new standing committee on Administration, consisting of the President, the Secretary and the Treasurer was authorized. A change was made whereby a member of another state or territorial medical society may be admitted to fellowship, with proper safeguards but with less delay than is now necessary.

At the same meeting 32 fifty-year fellows received pins, and the annual awards in appreciation of "diligent work in the medical school by one who best exemplifies those intangible qualities which serve to designate him as a good physician" were

presented to a student from each of the medical schools in Massachusetts. These men are Thomas F. Rafferty, of Lynn, Christopher M. Martin, of Jackson Heights, New York, and George C. Hamill, of Barrington, Illinois, representing respectively Tufts College Medical School, Harvard Medical School and Boston University School of Medicine.

The Annual Oration by Dr. Sara M. Jordan on "Medicine and the Doctor in Word and Epigram" represented a happy blend of scholarliness and entertainment; the Shattuck Lecture by Sir Alexander Fleming on "Twentieth Century Changes in the Treatment of Septic Infections" was learned and instructive. At the annual dinner on May 20 Dr. Thomas R. A. H. Davis, director of medical services for the Cook Islands, New Zealand, and Mrs. Davis, gave their stirring saga of men, women and children against the sea in their voyage across the Pacific in a small sailboat.

Dr. Frederic Hagler, of Springfield, was elevated to the presidency from his position as president-elect, Dr. Harvey A. Kelly, of Winthrop, was elected vice-president, Dr. Robert W. Buck, of Newton, was confirmed as Secretary, and Dr. Curtis C. Tripp, of New Bedford, was chosen president-elect for the coming year, Dr. Basil E. Barton, of West Roxbury, being elected orator.

The Woman's Auxiliary, meeting independently at the Harvard Club under the presidency of Mrs. George E. McCabe, put on the record five years of impressive achievement since its foundation. The president herself, establishing her own unique record for active leadership, admits to a year's total of 1400 letters written, 8000 miles traveled and at least one visit to each of the 16 districts where the ladies have asserted themselves to the point of forming auxiliaries. General accomplishments are noted in the fields of increased membership, increased subscriptions to *Today's Health*, nurse recruitment, civil-defense organization, legislative work, and in the publication of the *Bay Stater*.

The new officers are Mrs. James M. Ward, of Quincy, president; Mrs. A. J. A. Campbell, of Brighton, president-elect; Mrs. Sidney C. Wiggin, of Waban, first vice-president; Mrs. John C. Angley, of Bryantville, second vice-president; Mrs. Joseph V. Chatigny, of Taunton, recording secretary; Mrs. Thomas P. Devlin, of Stoneham, corresponding secretary; and Mrs. Erskine R. Pickwick, of Fitchburg, treasurer.

REGARDING PAYMENT OF DUES

THE year 1953 appears to be establishing an exceptionally poor record for the payment of Massachusetts Medical Society dues. As of May 21, 5633 fellows were eligible to receive the *Journal* by virtue of being in the good graces of the treasurer of the Society or, being retired, of having requested a free subscription. The total Society membership list was currently 7060; of over 400 retired fellows a majority were receiving the *Journal* by request. Subscriptions at a $4 rate, $1 less than active fellows are expected to pay, went to approximately 60 fellows in the armed forces as voted by the Council of the Society several years ago.

Comparisons are odious but occasionally interesting. In the corresponding week a year ago, with the total membership somewhat less than in the current year, 5967 fellows were on the eligible list; in 1951, the year in which the dues were increased, the comparable figure was 5628 but the total membership of the Society, since it has been increasing each year, was obviously still smaller.

Excluding 400-odd retired — or, as they should now be called senior fellows — whose dues are remitted, it becomes painfully apparent that on May 21 approximately 1000 fellows were delinquent in their dues and had, as a result, failed to receive their *Journals* for a matter of nearly two months. It is one of the penalties of living in a practical world that these sordid details should interpose themselves between the individual and his more intellectual interests; that even the artist should be a victim of the necessity for alimentation.

We are indebted to Dr. Jas. M. Scaife, of Claiborn Parish, Louisiana, for several very handsome specimens of calcareous concretions expectorated by a patient affected with consumption.

Boston M. & S. J., *June 15, 1853*

MASSACHUSETTS MEDICAL SOCIETY

AMERICAN MEDICAL EDUCATION FOUNDATION 1953 NEEDS

The average cost of training a doctor is $10,000. Tuition fees, raised 165 per cent since 1940, pay only one fifth of this cost.

Endowment income has shrunk. General university funds have been tapped to the limit. Funds from other sources must be found before irreparable harm is done.

These sources are only two: the government or private industry.

The National Fund for Medical Education represents industry's effort to find the money. The American Medical Education Foundation represents organized medicine's share in this effort.

Thirty-seven corporations like the Abbott Laboratories, General Mills, Eli Lilly, Charles Pfizer and Company, Time, Incorporated, and the Upjohn Company have contributed $10,000 to $100,000 each.

Sixty-six others like Allied Chemical and Dye Corporation, A. B. Dick Company, Hart, Schaffner and Marx, Mead Johnson Company and J. P. Stevens and Company have contributed $1,000 to $10,000 each.

Out of 200,000 doctors in the country, 7000 gave $407,000. Through the A. M. A. they painlessly contributed another $500,000 ($2.50 apiece) — a total of not quite $1,000,000. In 1953 this contribution should be doubled by the simple expedient of doubling the number of contributors.

Last year, only 54 Massachusetts physicians contributed a total of $2,390 directly to the Foundation. An unknown number have contributed directly to their own medical schools.

In Nebraska, 464 individual doctors gave a total of $49,221, largely owing to the energy and personal solicitation of Dr. Louis D. McGuire.

Pledge cards are available through the office of the secretary of the Massachusetts Medical Society, district secretaries, and through the A. M. A. offices, 535 North Dearborn Street, Chicago 10, Illinois. Fellows may allocate their pledges to their own medical schools.

ROBERT W. BUCK, M.D.
Secretary

DEATHS

CRAFT — Harry L. Craft, M.D., of Ashfield, died recently. He was in his seventy-fifth year.

Dr. Craft received his degree from University of Vermont College of Medicine in 1906. He was medical examiner for Franklin County, and served for twelve years as secretary-treasurer of the Franklin District Medical Society. He was a fellow of the American Medical Association.

He is survived by his widow, three sons and two brothers.

JORDAN — John F. Jordan, M.D., of Peabody, died on May 21. He was in his eighty-sixth year.

He received his degree from University of Michigan Medical School in 1900. He was a member of the staff of Thomas Hospital. He was an associate fellow of the American Medical Association.

He is survived by three sons and three daughters.

CORRESPONDENCE

THE ART OF MEDICINE

To the Editor: I have read the *Journal* regularly since 1949, my junior year in medical school, having enjoyed particularly the editorial page. You will find this letter to consist of a few paragraphs that I hope you will think are worth including in your publication.

The physician who is guided by the aphorism "Why speak, if you can keep silent?" knows a great deal about the true art of medicine. The seasoned doctor knows not only what to say to his patients, but also what to leave unsaid.

It has been pointed out that experience is of no ethical value; it is the name that men give to their mistakes. Experienced physicians are usually content to say very little to their patients other than giving general reassurance and simple, immediate instructions. They have learned the best way to avoid raising doubts and fears.

This is a difficult lesson for the young physician to learn. The value of silence is not immediately apparent; in fact, it is often foreign to him. As a student and house officer, he is taught to display his knowledge. Unfortunately, he is asked at times in the presence of the patient to mention differential diagnosis, or suggest possible diagnostic procedures. His instructors are careless about what they say in front of patients — in other words, of how they practice the art of medicine.

Besides the fact that keeping silent is new, it is also difficult because of the temptation every young doctor has to prove himself by displaying his knowledge to his new patients. He sometimes forgets that trusting patients credit the physician with cognizance of all possibilities, and that the patient is not the professor demanding a complete list of facts. He must remind himself that the patient is like a child asking for a simple answer or sometimes only a reassuring look or touch. Like the child, he is confused and bewildered when more is offered.

The art of medicine is difficult to define, and consequently difficult to teach. Yet it must not be neglected, for it is more important than the ability to make the most accurate diagnosis or prescribe the most effective antibiotic. The expensively educated young physician, though he may have academic qualifications beyond question, is indeed a poor physician until he has discovered the priceless gold of silence.

FRANK A. HOWARD, M.D. Lt. (J.G.) (MC) USNR
Green Cove Springs, Florida

NONCLINICAL NOTES

APPOINTMENT OF DR. CANDAU

On May 11, at Geneva, Switzerland, Dr. M. G. Candau, of Brazil, was appointed Director-General of the World Health Organization.

Dr. Candau succeeds Dr. Brock Chisholm, whose five-year term expires on July 21.

(*Notices on page xvii*)

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NOTICES

NEW YORK ACADEMY OF MEDICINE

The Twenty-Sixth Graduate Fortnight of the New York Academy of Medicine will be held October 19 through 30, the subject being "Disorders of the Blood and the Blood-Forming Organs." The program includes evening lectures, morning panel meetings, afternoon clinics and a scientific exhibit.

Nonfellows of the Academy will be sent registration cards for the entire program upon receipt of a check for $10, payable to the New York Academy of Medicine, and forwarded to the Academy, 2 East 103rd Street, New York 29, New York (the registration fee for the second week only is $5).

SOCIETY MEETINGS AND CONFERENCES

JUNE 26–28. American Academy of Dental Medicine. Page 664, issue of April 9.

JUNE 28–JULY 2. American Society of X-Ray Technicians. Page 480, issue of March 12.

JULY 8 AND 9. Seventh Annual Rocky Mountain Cancer Conference. Page 644, issue of April 9.

AUGUST 18–21. Third International Congress of Electroencephalography and Clinical Neurophysiology. Page 707, issue of April 16.

OCTOBER 19–30. New York Academy of Medicine. Notice above.

OCTOBER 28. New England Obstetrical and Gynecological Society. Page 868, issue of November 27.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JUNE 18

THURSDAY, JUNE 18

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

FRIDAY, JUNE 19

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.

*10:00 a.m.–1:00 p.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

*10:30–11:15 a.m. Diabetes Lecture. Dr. Elliott Joslin. New England Deaconess Hospital.

*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.

*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.

*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

SATURDAY, JUNE 20

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.

*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

*11:00 a.m.–12:00 m. Blood Clinic. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, JUNE 22

*8:00–9:00 a.m. Combined Medical and Surgical Rounds for Diabetic Surgery Cases. New England Deaconess Hospital.

*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.

*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

*7:00–9:00 p.m. Anesthesia Teaching Conference. Stearns Auditorium, New England Center Hospital.

TUESDAY, JUNE 23

*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.

*12:00 m.–1:00 p.m. Regular Grand Rounds of the Pediatric Department. Dowling Amphitheater, Boston City Hospital.

*12:00 m.–1:00 p.m. Pediatric Rounds, Burnham Memorial Hospital for Children, Massachusetts General Hospital.

*12:15–1:15 p.m. X-ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.

5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.

*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.

WEDNESDAY, JUNE 24

*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.

*12:00 m.–1:00 p.m. Clinicopathological Conference. (Children's Medical Center.) Jimmy Fund Building, 25 Binney Street.

12:30 p.m. Weekly Pathological Meeting. Joslin Amphitheater, New England Deaconess Hospital.

12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.

*2:00–3:00 p.m. Pediatric Conference for Practitioners. (Children's Medical Center.) Jimmy Fund Building, 25 Binney Street.

*4:00 p.m. Thoracic Conference. Held by Overholt Clinic. Harris Hall, New England Deaconess Hospital.

*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.

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1. Frost, L. H., and Jackson, R. L.: J. Pediat. 39: 585-592, 1951.

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